

# PATENT SPECIFICATION

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## (54) NEW BENZIMIDAZOLE DERIVATIVES, THEIR PREPARATION, AND THEIR USE IN AFFECTING GASTRIC ACID SECRETION

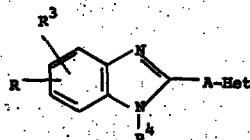
(71) We, AKTIEBOLAGET HASSLE, a Swedish Body Corporate, of Fack, S-431 20 Molndal 1, Sweden, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new heterocyclic compounds capable of affecting gastric acid secretion in mammals, to processes for their preparation, and to pharmaceutical compositions containing them.

It is desirable to obtain compounds which inhibit exogenously or endogenously stimulated gastric acid secretion, thereby useful for treating *inter alia* peptic ulcer disease.

It is also desirable to obtain compounds which stimulate gastric acid secretion, thereby useful for treating digestive disturbances related to low gastric acid production in the intestinal tract.

According to the present invention, there are provided compounds of the formula I:



(I)

wherein R and R<sup>3</sup>, which may be the same or different, each represents hydrogen, alkyl, halogen, nitro, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl or acyl, R<sup>4</sup> is hydrogen, acyl or carboalkoxy, A is —SCH<sub>2</sub>— or —SCH(CH<sub>3</sub>)—, whereby the sulphur atom is bound to the benzimidazolyl group, and Het is optionally substituted 2-quinolyl, or 2-pyridyl, provided that when Het is 2-pyridyl, A is —SCH<sub>2</sub> and R<sup>4</sup> is hydrogen, R and R<sup>3</sup> are not both hydrogen, one is not

5—CH<sub>3</sub> if the other is 6—CH<sub>3</sub>, one is not hydrogen if the other is 5—NO<sub>2</sub> or 5—Cl; and acid addition salts thereof.

Alkyl R and R<sup>3</sup> of formula I are suitably alkyl having up to 7 carbon atoms, preferably up to 4 carbon atoms. Thus alkyl R may be methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl.

Halogen R and R<sup>3</sup> are fluoro, iodo, bromo or chloro, preferably bromo or chloro.

Carboxy R and R<sup>3</sup> are the group HOOC—.

Carboalkoxy R and R<sup>3</sup> are the groups alkyl-O—OC—, wherein the alkyl group has up to 4 carbon atoms, preferably up to 2 carbon atoms. Carboalkoxy R and R<sup>3</sup> are e.g. carbomethoxy (CH<sub>3</sub>OOC—) and carboethoxy (C<sub>2</sub>H<sub>5</sub>OOC—).

Carboalkoxy alkyl R and R<sup>3</sup> are the groups alkylOOC-alkyl<sup>1</sup>—, wherein the alkyl group has up to 4 carbon atoms, preferably up to 2 carbon atoms, and the alkyl<sup>1</sup> group has up to 4 carbon atoms, preferably up to 2 carbon atoms, e.g.

carbomethoxymethyl (CH<sub>3</sub>OOCCH<sub>2</sub>—), carbomethoxyethyl (CH<sub>3</sub>OOCCH<sub>2</sub>CH<sub>2</sub>—), carbethoxymethyl (C<sub>2</sub>H<sub>5</sub>OOCCH<sub>2</sub>—) and carbethoxyethyl (C<sub>2</sub>H<sub>5</sub>OOCCH<sub>2</sub>CH<sub>2</sub>—).

Carbamoyl R and R<sup>3</sup> are the group H<sub>2</sub>NCO—.

Carbamoylalkyl R and R<sup>3</sup> are the groups H<sub>2</sub>NCOalkyl—, wherein the alkyl group has up to 4 carbon atoms preferably up to 2 carbon atoms, e.g. carbamoylmethyl (H<sub>2</sub>NCOCH<sub>2</sub>—), and carbamoylethyl (H<sub>2</sub>NCOCH<sub>2</sub>CH<sub>2</sub>—).

Alkoxy R and R<sup>3</sup> are suitably alkoxy groups having up to 5 carbon atoms, preferably up to 3 carbon atoms, e.g. methoxy, ethoxy, n-propoxy and isopropoxy.

Hydroxyalkyl R and R<sup>3</sup> have suitably up to 7 carbon atoms, preferably up to 4 carbon atoms and are straight or branched, e.g.

hydroxymethyl,  $\text{HOCH}_2 \cdot (\text{CH}_2)_3 \cdot \text{CH}_2-$ ,  
 $\text{HOCH}_2\text{CH}_2-$  or  $\text{HOCH}_2 \cdot (\text{CH}_2)_2 \cdot \text{C}-$ .

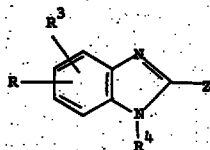
Acyl R and R<sup>3</sup> have preferably up to 4 carbon atoms, e.g. formyl, acetyl, or propionyl ( $\text{HCO}-$ ,  $\text{CH}_3\text{CO}-$ ,  $\text{CH}_3\text{CH}_2\text{CO}-$ ).

Acyl R<sup>4</sup> has preferably up to 4 carbon atoms and is e.g. formyl ( $\text{HCO}-$ ), acetyl ( $\text{CH}_3\text{CO}-$ ) or propionyl ( $\text{CH}_3\text{CH}_2\text{CO}-$ ).

Carboalkoxy R<sup>4</sup> is the group  
 $\text{alkyl-O-OC}-$ ,  
 wherein the alkyl group has up to 4 carbon atoms, preferably up to 2 carbon atoms, and is e.g. carbomethoxy ( $\text{CH}_3\text{OOC}-$ ), or carbethoxy ( $\text{C}_2\text{H}_5\text{OOC}-$ ).

The heterocyclic group Het may be further substituted with alkyl or halogen. Such alkyl groups are preferably C<sub>1</sub>-C<sub>3</sub> alkyl groups such as methyl, ethyl or propyl. Such halogen substituents are preferably chloro or bromo.

The compounds of formula I above may be prepared by reacting a compound of the formula IV



(IV)

wherein R and R<sup>3</sup> are as defined above and Z is SH or a reactive esterified hydroxy group, with a compound of the formula V



wherein Het is as defined above and Z<sup>1</sup> is a reactive esterified hydroxy group, or SH respectively.

The reactive, esterified hydroxy group can be a hydroxy group esterified with a strong, inorganic or organic acid, preferably a hydrohalic acid, such as hydrochloric acid, hydrobromic acid, or hydroiodic acid, or with sulphuric acid or a strong organic sulphonic acid such as a strong aromatic acid, e.g. benzenesulphonic acid, 4-bromobenzenesulphonic acid or 4-toluenesulphonic acid. Thus Z and Z<sup>1</sup> are preferably chloro, bromo or iodo.

Depending on the process conditions and the starting material the end product is obtained either as the free base or in the form of its acid addition salt, which is included in the scope of the invention. Thus, for example, basic, neutral or mixed salts may be obtained as well as hemiamino, sesqui- or polyhydrates. The acid addition salts of the new compounds may, in a manner known *per se*, be transformed into the free base using e.g. basic agents such as alkali or ion exchangers. On the other hand, the free bases obtained can form salts with organic or inorganic acids. In the preparation of acid addition salts, preferably acids are used which form therapeutically acceptable

salts. Such acids are e.g. hydrohalic acids, sulphuric acid, phosphoric acid, nitric acid, perchloric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxy or sulphonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic or pyruvic acid, phenylacetic, benzoic, *p*-aminobenzoic, anthranilic, *p*-hydroxybenzoic, salicylic or *p*-aminosalicylic acid, embonic acid, methanesulphonic, ethanesulphonic, hydroxyethanesulphonic, ethylenesulphonic acids, halogen-benzenesulphonic, toluenesulphonic, naphthylsulphonic acids or sulphanilic acid; methionine, tryptophane, lysine or arginine.

These or other salts of the new compounds e.g. picrates, may serve as purifying agents of the free bases obtained by the process described above. The free base can be transformed into a salt, this is separated from the reaction product and the base is then liberated from the salt. The present invention includes both the free bases and their therapeutically acceptable and other acid addition salts. Certain compounds of the invention contain an asymmetric carbon atom and may be present as an isomer mixture (racemate mixture) or as optically pure isomers.

The racemate obtained can be separated according to known methods, e.g. by recrystallisation from an optically active solvent, by means of microorganisms, or by a reaction with optically active acids forming salts of the compound and separating the salts thus obtained, e.g. by means of their different solubility in the diastereomers, from which the antipodes by the influence of a suitable agent may be set free. Suitable optically active acids are e.g. L- and D-forms of tartaric acid, di-*o*-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid or china acid (quinic acid). Preferably the more active part of the two antipodes is isolated.

In clinical use, the compounds of the invention are administered normally orally, rectally or by injection in the form of a pharmaceutical preparation, which contains a compound of the invention as an active component, either as free base or as pharmaceutically acceptable, non-toxic acid addition salt, e.g. the hydrochloride, lactate, acetate or sulphamate, in combination with a pharmaceutically acceptable carrier and such preparations form a further aspect of the present invention. In this description, references to the free base include a reference to the pharmaceutically acceptable salts except where the context clearly does not permit this. The carrier may be a solid, semi-solid or liquid diluent or a capsule. Usually the amount of active compound is 0.1 to 95% by weight of the preparation, suitably 0.5 to 20% by weight in preparations for injection and 2 to 50% by weight in solid preparations for oral administration.

In the preparation of pharmaceutical preparations in the form of dosage units for oral administration the compound selected may be mixed with a solid, pulverulent carrier, e.g. with lactose, saccharose, sorbitol, mannitol, starch, such as potato starch, corn starch or amylopectin, cellulose derivatives or gelatine, as well as with an anti-friction agent, e.g. magnesium stearate, calcium stearate or polyethylene glycol waxes, and be pressed into tablets. If coated tablets are wanted, the above prepared core may be coated with concentrated solution of sugar and/or with gum arabicum, gelatine, talc or titanium dioxide. The tablets may also be coated with a lacquer dissolved in an easily volatile organic solvent or mixture of solvents. To this coating, a dye may be added in order to distinguish easily between tablets with different active compounds or with different amounts of the active compound present.

In the preparation of soft gelatine capsules (pearl-shaped, closed capsules), which consist of gelatine and e.g. glycerine or in the preparation of similar closed capsules the active compound is mixed with a vegetable oil. Hard gelatine capsules may contain granules of the active compound in combination with a solid, pulverulent carrier, e.g. lactose, saccharose, sorbitol, mannitol, starch (e.g. potato starch, corn starch or amylopectin), cellulose derivatives or gelatine.

Dosage units for rectal administration may be prepared in the form of suppositories, which contain the active substance in a mixture with a neutral fat base, or they may be prepared in the form of gelatin-rectal capsules which contain the active substance in a mixture with a vegetable oil or paraffin oil.

Liquid preparations for oral administration may be present in the form of syrups or suspensions, e.g. solutions containing from 0.2% by weight to 20% by weight of the active substance selected, the residue consisting of sugar and a mixture of ethanol, water, glycerol and propylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent.

Solutions for parenteral administration by injection may be prepared as an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active compound, preferably in a concentration from 0.5% by weight to 0.10% by weight. These solutions may also contain stabilising agents and/or buffering agents and may suitably be available in different dosage unit ampoules.

The preparation of pharmaceutical tablets for peroral use is carried out in accordance with the following method:

The solid substances included are ground or sieved to a selected particle size. The binding agent is homogenised and suspended in

a selected amount of solvent. The therapeutic compound and necessary auxiliary agents are continuously mixed with the binding agent solution and are moistened so that the solution is uniformly divided in the mass without over-moistening. The amount of solvent is usually chosen so that the mass has a consistency reminiscent of wet snow. The moistening of the pulverulent mixture with the binding agent solution causes the particles to aggregate together and the granulating process is carried out in a way such that the mass is pressed through a stainless steel net having a mesh size of about 1 mm. The mass is then placed in thin layers on a tray to be dried in a drying cabinet. This drying takes place over 10 hours and has to be standardised carefully as the moisture content of the granulate is of utmost importance for the following process and for the character of the tablets. Drying in a fluid bed is also possible. In this case, the mass is not put on a tray but instead, is poured into a container having a net bottom.

After the drying step, the granules are sieved so that the desired particle size is obtained. Under certain circumstances, fine powder has to be removed.

To the so-called final mixture, disintegrating, anti-friction agents and anti-adhesive agents are added and the mass then has the right composition for the tableting step.

A cleaned tablet punching machine is used having the desired set of punches and dies, and the necessary adjustment for the desired weight of the tablets and the degree of compression is carried out. The weight of the tablet is decisive for the size of the dose in each tablet and is calculated starting from the amount of therapeutic agent in the granules. The degree of compression affects the size of the tablet, its strength and its ability to disintegrate in water. The balancing of requirements for the two latter properties normally indicates a compression pressure of 0.5 to 5 ton. When the right adjustment is set, the preparation of tablets begins, which can be carried out at a rate of 20,000 to 200,000 tablets per hour. The pressing of the tablets requires different times and depends on the size of the batch.

The tablets are freed from adhering pulverulent material and are then stored in closed packages until required.

Many tablets, especially those which are rough or bitter, are coated e.g. with a layer of sugar.

The tablets are usually packed by machines having an electronic counting device into packages which may be glass or plastic gallipots, or boxes, tubes or specific dosage adapted packages.

The daily dose of the active substance varies and depends on the route of administration, but, as a general rule, it is 100 to 400 mg/day

of active substance by peroral administration and 5 to 20 mg/day by intravenous administration.

The following Examples illustrate the invention. Temperature is given in degree Celsius.

The starting materials in the Examples found below were prepared in accordance with the following procedure:

A 1,2-diamino compound, e.g. *o*-phenylenediamine was reacted with potassiummethylxanthate (according to Org. Synth. vol. 30 p. 56) to form a 2-mercaptobenzimidazole.

2-Chloromethylpyridine was prepared by reacting 2-hydroxymethylpyridine with thionylchloride (according to Arch. Pharm. vol. 26 pp. 448—451 (1956)).

2-Chloromethylbenzimidazole was prepared by condensating *o*-phenylenediamine with chloroacetic acid.

#### Example 1.

0.1 moles of 4-methyl-2-mercaptobenzimidazole were dissolved in 20 ml of water and 200 ml of ethanol containing 0.2 moles of sodium hydroxide. 0.1 moles of 2-chloromethylpyridine hydrochloride were added and the mixture was refluxed for 2 hours. The sodium chloride formed was filtered off and the solution was evaporated *in vacuo*. The residue was dissolved in acetone and was treated with active carbon. An equivalent amount of concentrated hydro-

chloric acid was added, and the monohydrochloride of 2-[2-pyridylmethylthio]-4-methylbenzimidazole was isolated. Yield 0.05 mole, melting point 137°C.

#### Examples 2 to 16.

The preparation was carried out in accordance with Example 1 above using the appropriate benzimidazole and appropriate pyridine or quinoline. The compounds prepared are listed in the following Table I.

#### Example 17.

13.5 g (0.05 moles) of 2-[2-pyridylmethylthio]-benzimidazole hydrochloride, 3.9 g (0.05 moles) of acetyl chloride, and 10.1 g (0.1 moles) of triethylamine were dissolved in 100 ml of acetonitrile. The mixture was heated in a 40°C-waterbath for 30 minutes. After cooling the crystals formed were filtered off which were suspended in water in order to dissolve the triethylamine hydrochloride. The residue, 2-[2-pyridylmethylthio]-N-acetylbenzimidazole, was filtered off. Yield 7.2 g (51%) m.p. 119—124°C as base.

#### Example 18.

2-[2-pyridylmethylthio]-N-methoxycarbonylbenzimidazole was prepared as described in Example 17 above, but replacing the acetyl chloride by methylchloroformate.

TABLE I

Compounds of formula I prepared as described in Examples 1 to 18.



| Ex. | R <sup>3</sup>    | R                                  | R <sup>4</sup> | A                   | Het                 | M.P. °C         |
|-----|-------------------|------------------------------------|----------------|---------------------|---------------------|-----------------|
| 1   | H                 | 4-CH <sub>3</sub>                  | H              | -SCH <sub>2</sub> - | 2-pyridyl           | 137-183 (2.HCl) |
| 2   | 6-CH <sub>3</sub> | 4-CH <sub>3</sub>                  | H              | -SCH <sub>2</sub> - | 2-pyridyl           | 230 (HCl)       |
| 3   | H                 | 5-C <sub>2</sub> H <sub>5</sub>    | H              | -SCH <sub>2</sub> - | 2-pyridyl           | 180 (HCl)       |
| 4   | 6-Cl              | 4-CH <sub>3</sub>                  | H              | -SCH <sub>2</sub> - | 2-pyridyl           | 180 (HCl)       |
| 5   | H                 | 5-OCH <sub>3</sub>                 | H              | -SCH <sub>2</sub> - | 2-pyridyl           | 155-195 (2.HCl) |
| 6   | H                 | 5-OH                               | H              | -SCH <sub>2</sub> - | 2-pyridyl           | 190-200 (HCl)   |
| 7   | H                 | 5-COCH <sub>3</sub>                | H              | -SCH <sub>2</sub> - | 2-pyridyl           | 144 (base)      |
| 8   | H                 | 5-COOH                             | H              | -SCH <sub>2</sub> - | 2-pyridyl           | 268 (base)      |
| 9   | H                 | 5-COOC <sub>2</sub> H <sub>5</sub> | H              | -SCH <sub>2</sub> - | 2-pyridyl           | 180-190 (2.HCl) |
| 10  | H                 | H                                  | H              | -SCH <sub>2</sub> - | 2-(6-methylpyridyl) | 121 (HCl)       |
| 11  | H                 | H                                  | H              | -SCH <sub>2</sub> - | 2-(6-chloropyridyl) | 145 (base)      |
| 12  | H                 | H                                  | H              | -SCH <sub>2</sub> - | 2-(4-chloropyridyl) |                 |
| 13  | H                 | H                                  | H              | -SCH <sub>2</sub> - | 2-(5-methylpyridyl) | 134 (HCl)       |
| 14  | H                 | H                                  | H              | -SCH <sub>2</sub> - | 2-quinolyl          | 144-163 (HCl)   |
| 15  | H                 | 5-CH <sub>2</sub> OH               | H              | -SCH <sub>2</sub> - | 2-pyridyl           |                 |

TABLE I (Continued)

| Ex. | R <sup>2</sup> | R | R <sup>4</sup>     | A                        | Het       | M.P. °C        |
|-----|----------------|---|--------------------|--------------------------|-----------|----------------|
| 16  | H              | H | H                  | -S-CH(CH <sub>3</sub> )- | 2-pyridyl | 165 (HCl)      |
| 17  | H              | H | COCH <sub>3</sub>  | -SCH <sub>2</sub> -      | 2-pyridyl | 119-124 (base) |
| 18  | H              | H | COOCH <sub>3</sub> | -SCH <sub>2</sub> -      | 2-pyridyl | 78 (base)      |

**BIOLOGICAL EFFECT**

The compounds of the invention possess valuable therapeutic properties as gastric acid affecting compounds.

Experiments were carried out on dogs using a modified perfusion technique.

The stomach of an anaesthetized dog was fitted with one tube through its oesophagus for instillation of fluid and another tube *via* the ligated pylorus through the duodenum for drainage of fluid. Saline was introduced at the rate of 5 ml/kg body weight, and was changed every 15 minutes.

The samples collected were titrated to pH 7.0 with 0.04 N NaOH using a Radiometer automatic titrator, and the acid output per 15 minutes was calculated (collection periods).

Gastric acid secretion was induced by pentagastrin in 1-2 µg/kg an hour, giving a submaximal secretory response.

Test compounds in 0.5% Methocel (Registered Trade Mark) suspension were given into the duodenum close to the ligation at least 2 hours following onset of stimulation, when the secretion had reached a steady level for three consecutive 15 minute periods.

The gastric secretion response was noted, whereby it was found that all compounds of the Examples above were gastric acid secretion inhibitors.

**Example 19.**

A syrup containing 2% (weight per volume) of active substance was prepared from the following ingredients:

2-[2-(pyridylmethyl)thio]-4-

methylbenzimidazole HCl

Saccharine

Sugar

Glycerine

Flavouring agent

Ethanol 96%

Distilled water

Sugar, saccharine and the thio-ether salt were dissolved in 60 g of warm water. After cooling glycerine and a solution of flavouring agents dissolved in ethanol were added. Water was then added to the mixture up to 100 ml.

**Example 20.**

2 - [5 - methyl - 2 - pyridyl - methylthio] - benzimidazole HCl (250 g) was mixed with lactose (175.8 g), potato starch (169.7 g) and colloidal silicic acid (32 g). The mixture was moistened with a 10% solution of gelatine and was granulated through a 12 mesh sieve. After drying, the granulate, potato starch (160 g), talc (50 g) and magnesium stearate (5 g) were mixed together and the mixture so obtained pressed into tablets

(10,000) each of which contain 25 mg of substance. The tablets are provided with a breaking score to give a dose other than 25 mg.

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#### Example 21.

Granules were prepared as described in Example 20 from active compound (250 g), lactose (175.9 g) and an alcoholic solution of polyvinylpyrrolidone (25 g). After the drying step, the granules were mixed with talc (25 g), potato starch (40 g) and magnesium stearate (2.50 g) and were pressed into 10,000 biconvex tablets. These tablets were first coated with a 10% alcoholic solution of shellac and then with an aqueous solution containing saccharose (45%), gum arabicum (5%), gelatine (4%) and dyestuff (0.2%). Talc powder or sugar was used for powdering after the first five coatings. The tablet was finally coated with a 66% sugar syrup and polished with a 10% carnauba wax solution in carbon tetrachloride.

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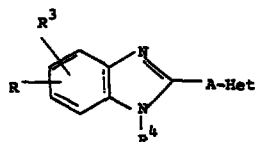
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#### Example 22.

Active compound (1 g), sodium chloride (0.8 g) and ascorbic acid (0.1 g) were dissolved in sufficient distilled water to give 100 ml of solution. This solution, which contains 10 mg of active substance in each ml, was used in filling ampoules, which were sterilised by heating at 120°C for 20 minutes.

#### WHAT WE CLAIM IS:—

1. A compound of formula I:



(I)

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wherein R and R<sup>3</sup>, which may be the same or different, each represents hydrogen, alkyl, halogen, nitro, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl or acyl, R<sup>4</sup> is hydrogen, acyl or carboalkoxy, A is —SCH<sub>2</sub>— or SCH(CH<sub>3</sub>)—, whereby the sulphur atom is bound to the benzimidazolyl group, and Het is optionally substituted 2-quinolyl or 2-pyridyl, provided that when Het is 2-pyridyl, A is —SCH<sub>2</sub>—, and R<sup>4</sup> is hydrogen, R and R<sup>3</sup> are not both hydrogen, one is not 5—CH<sub>3</sub> if the other is 6—CH<sub>3</sub>, one is not hydrogen if the other is 5—NO<sub>2</sub> or 5—Cl; and acid addition salts thereof.

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2. A compound according to claim 1, wherein R is hydrogen, hydroxy, methyl, ethyl, methoxy, acetyl, carboxy or carbethoxy, R<sup>3</sup> is hydrogen, methyl or chloro, R<sup>4</sup> is hydrogen, acetyl or carbomethoxy, A is —SCH<sub>2</sub>— and Het is 2-pyridyl which may be substituted

with methyl, or chloro or 2-quinolyl; or a therapeutically acceptable acid addition salt thereof.

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3. A compound according to claim 1, wherein R and R<sup>3</sup> are hydrogen, R<sup>4</sup> is hydrogen, A is —S—CH(CH<sub>3</sub>)— and Het is 2-pyridyl; or a therapeutically acceptable acid addition salt thereof.

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4. 2 - [2 - pyridylmethylthio] - 4 - methyl - benzimidazole.

5. 2 - [2 - pyridylmethylthio] - 4,6 - dimethyl - benzimidazole.

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6. 2 - [2 - pyridylmethylthio] - 5 - ethyl - benzimidazole.

7. 2 - [2 - pyridylmethylthio] - 4 - methyl - 6 - chloro - benzimidazole.

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8. 2 - [2 - pyridylmethylthio] - 5 - methoxy - benzimidazole.

9. 2 - [2 - pyridylmethylthio] - 5 - hydroxy - benzimidazole.

10. 2 - [2 - pyridylmethylthio] - 5 - acetyl - benzimidazole.

75

11. 2 - [2 - pyridylmethylthio] - 5 - carbony - benzimidazole.

12. 2 - [2 - pyridylmethylthio] - 5 - carbethoxy - benzimidazole.

80

13. 2 - [6 - methyl - 2 - pyridylmethylthio] - benzimidazole.

14. 2 - [6 - chloro - 2 - pyridylmethylthio] - benzimidazole.

15. 2 - [4 - chloro - 2 - pyridylmethylthio] - benzimidazole.

85

16. 2 - [5 - methyl - 2 - pyridylmethylthio] - benzimidazole.

17. 2 - [2 - quinolylmethylthio] - benzimidazole.

90

18. 2 - [2 - pyridylmethylthio] - 5 - hydroxymethyl - benzimidazole.

19. 2 - [1 - (2 - pyridyl) - ethylthio] - benzimidazole.

20. 2 - [2 - pyridylmethylthio] - 1 - acetyl - benzimidazole.

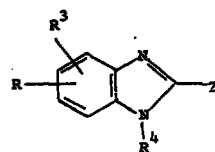
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21. 2 - [2 - pyridylmethylthio] - 1 - methoxycarbonyl - benzimidazole.

22. The compound as claimed in any one of claims 4 to 21, in the form of a therapeutically acceptable acid addition salt.

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23. A process for preparing a compound as defined in claim 1, which comprises reacting a compound of formula I'



(IV)

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wherein R, R<sup>3</sup> and R<sup>4</sup> are as defined in claim 1 and Z is —SH, or a reactive esterified hydroxy group, with a compound of formula V

Z'—CH<sub>2</sub>Het or Z'—CH(CH<sub>3</sub>)Het (V)



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(10,000) each of which contain 25 mg of substance. The tablets are provided with a breaking score to give a dose other than 25 mg.

#### Example 21.

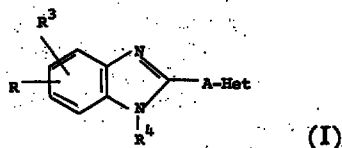
Granules were prepared as described in Example 20 from active compound (250 g), lactose (175.9 g) and an alcoholic solution of polyvinylpyrrolidone (25 g). After the drying step, the granules were mixed with talc (25 g), potato starch (40 g) and magnesium stearate (2.50 g) and were pressed into 10,000 biconvex tablets. These tablets were first coated with a 10% alcoholic solution of shellac and then with an aqueous solution containing saccharose (45%), gum arabicum (5%), gelatine (4%) and dyestuff (0.2%). Talc powder or sugar was used for powdering after the first five coatings. The tablet was finally coated with a 66% sugar syrup and polished with a 10% carnauba wax solution in carbon tetrachloride.

#### Example 22.

Active compound (1 g), sodium chloride (0.8 g) and ascorbic acid (0.1 g) were dissolved in sufficient distilled water to give 100 ml of solution. This solution, which contains 10 mg of active substance in each ml, was used in filling ampoules, which were sterilised by heating at 120°C for 20 minutes.

#### WHAT WE CLAIM IS:—

1. A compound of formula I:



wherein R and R<sup>3</sup>, which may be the same or different, each represents hydrogen, alkyl, halogen, nitro, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl or acyl, R<sup>4</sup> is hydrogen, acyl or carboalkoxy, A is —SCH<sub>2</sub>— or SCH(CH<sub>3</sub>)—, whereby the sulphur atom is bound to the benzimidazolyl group, and Het is optionally substituted 2-quinolyl or 2-pyridyl, provided that when Het is 2-pyridyl, A is —SCH<sub>2</sub>—, and R<sup>4</sup> is hydrogen, R and R<sup>3</sup> are not both hydrogen, one is not 5—CH<sub>3</sub> if the other is 6—CH<sub>3</sub>, one is not hydrogen if the other is 5—NO<sub>2</sub> or 5—Cl; and acid addition salts thereof.

2. A compound according to claim 1, wherein R is hydrogen, hydroxy, methyl, ethyl, methoxy, acetyl, carboxy or carbethoxy, R<sup>3</sup> is hydrogen, methyl or chloro, R<sup>4</sup> is hydrogen, acetyl or carbomethoxy, A is —SCH<sub>2</sub>— and Het is 2-pyridyl which may be substituted

with methyl, or chloro or 2-quinolyl; or a therapeutically acceptable acid addition salt thereof.

3. A compound according to claim 1, wherein R and R<sup>3</sup> are hydrogen, R<sup>4</sup> is hydrogen, A is —S—CH(CH<sub>3</sub>)— and Het is 2-pyridyl; or a therapeutically acceptable acid addition salt thereof.

4. 2 - [2 - pyridylmethylthio] - 4 - methyl - benzimidazole.

5. 2 - [2 - pyridylmethylthio] - 4,6 - dimethyl - benzimidazole.

6. 2 - [2 - pyridylmethylthio] - 5 - ethyl - benzimidazole.

7. 2 - [2 - pyridylmethylthio] - 4 - methyl - 6 - chloro - benzimidazole.

8. 2 - [2 - pyridylmethylthio] - 5 - methoxy - benzimidazole.

9. 2 - [2 - pyridylmethylthio] - 5 - hydroxy - benzimidazole.

10. 2 - [2 - pyridylmethylthio] - 5 - acetyl - benzimidazole.

11. 2 - [2 - pyridylmethylthio] - 5 - carbonyl - benzimidazole.

12. 2 - [2 - pyridylmethylthio] - 5 - carbethoxy - benzimidazole.

13. 2 - [6 - methyl - 2 - pyridylmethylthio] - benzimidazole.

14. 2 - [6 - chloro - 2 - pyridylmethylthio] - benzimidazole.

15. 2 - [4 - chloro - 2 - pyridylmethylthio] - benzimidazole.

16. 2 - [5 - methyl - 2 - pyridylmethylthio] - benzimidazole.

17. 2 - [2 - quinolylmethylthio] - benzimidazole.

18. 2 - [2 - pyridylmethylthio] - 5 - hydroxymethyl - benzimidazole.

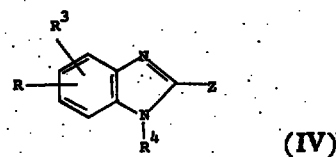
19. 2 - [1 - (2 - pyridyl) - ethylthio] - benzimidazole.

20. 2 - [2 - pyridylmethylthio] - 1 - acetyl - benzimidazole.

21. 2 - [2 - pyridylmethylthio] - 1 - methoxycarbonyl - benzimidazole.

22. The compound as claimed in any one of claims 4 to 21, in the form of a therapeutically acceptable acid addition salt.

23. A process for preparing a compound as defined in claim 1, which comprises reacting a compound of formula IV



wherein R, R<sup>3</sup> and R<sup>4</sup> are as defined in claim 1 and Z is —SH, or a reactive esterified hydroxy group, with a compound of formula V



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wherein Het is as defined in claim 1 and Z<sup>1</sup> is a reactive esterified hydroxy group, or —SH, respectively.

5 24. A process according to claim 23, wherein the compound is prepared in the form of an isomeric mixture and the mixture is separated into the pure isomers.

10 25. A process according to claim 24, wherein the compound is prepared in the form of a racemate and a laevo-rotating stereo isomer and/or a dextro-rotating stereo isomer is isolated from the racemate.

15 26. A process according to any one of claims 23 to 25 wherein the compound is prepared in the form of a free base and is then converted into an acid addition salt.

27. A process according to claim 26, wherein the salt is a therapeutically acceptable acid addition salt.

20 28. A process according to any one of claims 23 to 25 wherein the compound is prepared in the form of an acid addition salt and the salt is then converted into the free base.

25 29. A process according to any one of claims 23 to 28 wherein the reactive esterified hydroxy group is a halogen atom.

30 30. A process according to claim 29, wherein the halogen atom is a chlorine atom.

30 31. A process according to claim 23, substantially as hereinbefore described with reference to any one of Examples 1 to 18.

35 32. A compound of formula I, or an acid addition salt thereof, whenever prepared by a process as claimed in any one of claims 23 to 31.

40 33. A compound of formula I, or a therapeutically acceptable acid addition salt thereof, whenever prepared by a process as claimed in any one of claims 23 to 25 or 27 to 31.

34. A pharmaceutical preparation, comprising at least one compound or therapeutically acceptable acid addition salt thereof according to any one of claims 1 to 22 or 33 in association with a pharmaceutically acceptable carrier.

35. A preparation according to claim 34, containing 0.1 to 95% by weight of the compound or salt.

36. A preparation according to claim 35, in a form suitable for administration by injection containing 0.5 to 20% by weight of the compound or salt.

37. A preparation according to claim 35, in a form suitable for parenteral application comprising an aqueous solution containing 0.5 to 10% by weight of a water soluble salt of the compound.

38. A preparation according to claim 35, in a solid form suitable for oral administration and containing 2 to 50% by weight of the compound or salt.

39. A preparation according to claim 35, in a liquid form suitable for oral administration and containing 0.2 to 20% by weight of the compound or salt.

40. A preparation according to any one of claims 34 to 38, wherein the compound or salt is a compound according to any one of claims 4 to 21, or a pharmaceutically acceptable non-toxic acid addition salt thereof.

41. A preparation according to claim 34, substantially as hereinbefore described with reference to any one of Examples 19—22.

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