REQUEST FOR A STANDARD PATENT
AND NOTICE OF ENTITLEMENT

The Applicant identified below requests the grant of a patent to the
nominated person identified below for an invention described in the
accompanying standard complete patent specification.

[70,71] Applicant and Nominated Person:

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[54] Invention Title:

NOVEL DERIVATIVES OF BENZIMIDAZOLE, THEIR PREPARATION, AND THEIR USE
AS MEDICAMENTS

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Details of basic application(s):

90 09563 FRANCE FR 26 July 1990

Applicant states the following:

The nominated person is the assignee of the actual inventor(s)
The basic convention application was/were the first made in a
convention country in respect of the invention the subject of
the application.
The nominated person is not an opponent or eligible person
described in Section 33-36 of the Act.

24 July 1991

Laboratorios Del Dr. Esteve, S.A.
By PHILLIPS ORMONDE & FITZPATRICK
Patent Attorneys
By

David Fitzpatrick

Oz Ref : 223165
5999q
1. Novel compounds derived from benzimidazole characterized in that they correspond to the general formula I, and their therapeutically acceptable salts,

\[
\text{I} \\
\begin{array}{c}
\text{N} \\
\text{CH}_{2}\text{N} \\
\text{CH}_{2}\text{CCHCH} \\
\text{R}_{1} \quad \text{R}_{2} \\
\text{CH}_{2}\text{CH}_{2}\text{OCH}_{2}\text{CH}_{3}
\end{array}
\]

in which:
- \(R_{1}\) and \(R_{2}\), equal or different, represent a hydrogen atom, a halogen, a lower alkyl radical, a hydroxy radical, an alkoxy radical, an alkyl carboxylate radical, an aryl or substituted aryl radical,
- \(n\) can have the values 0 or 1,
- \(m\) can have the values 2 to 4,
- \(X, Y, Z\) and \(W\) are equal or different, and even form part of the same ring, aromatic or not, represent a nitrogen atom or a carbon atom bonded to a hydrogen
atom, to a halogen or to another alkyl, aryl, carboxyalkyl, carboxylic, hydroxyl, alkylhydroxy, sulfonic, or alkylsulfonic radical.

6. Method of practising prophylaxis and of treating various allergic disorders caused by histamine, utilizing a derivative of the general formula I and its physiologically acceptable salts, according to one of claims 1 and 2.
Name of Applicant:
Laboratorios Del Dr. Esteve, S.A.

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Maria Rosa Cuberes-Altisent
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Patent and Trade Mark Attorneys
367 Collins Street
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Invention Title:
NOVEL DERIVATIVES OF BENZIMIDAZOLE, THEIR PREPARATION, AND THEIR USE AS MEDICAMENTS

Our Ref: 223165
POF Code: 2975/113338

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):
NOVEL DERIVATIVES OF BENZIMIDAZOLE, THEIR PREPARATION, AND THEIR USE AS MEDICAMENTS

BACKGROUND OF THE INVENTION

The present invention relates to novel derivatives of benzimidazole, their process of preparation as well as their use as medicaments.

The compounds according to the present invention correspond to the general formula I

in which:

- \( R_1 \) and \( R_2 \), equal or different, represent a hydrogen atom, a halogen, a lower alkyl radical, a hydroxy radical, an alkoxy radical, an alkyl carboxylate radical, an aryl or substituted aryl,
- \( n \) may have the values 0 or 1,
- \( m \) may have the values 2 to 4,
- \( X, Y, Z \) and \( W \), equal or different, and even forming part of another ring, aromatic or not, represent a nitrogen atom or a carbon atom linked to a hydrogen atom, a halogen or another alkyl, aryl, carboxyalkyl, carboxylic, hydroxyl, alkylhydroxy, sulfonic and alkylsulfonic radical.
In the scientific literature derivatives of benzimidazole are already known with different biological activities, like for example, analgesic and antiinflammatory activity (Japan Kokai 75, 126, 682), gastric antisecretory activity (EP 246,126 and EP 5129); antihistaminic activity (J. Jilek et al., Collect. Czech. Chem. Commun. 1988, 53, 870-83; US Patent 4,200,641; Drugs of the Future, VII; 10-1, 1982; R. Iemura et al., J. Med. Chem., 1987, 24, 31-37). The compounds according to the present invention are novel derivatives of benzimidazole, actually 1-(2-ethoxyethyl)-2-(alkylpiperazinylalkylzoles) benzimidazole. We have discovered that these novel derivatives have very good antihistaminic activity and they do not have side effects on the central nervous system.

The novel derivatives of general formula I may be prepared, according to the invention, according to any one of the following methods:

**Method A.** - By reaction of the compound of the general formal IIa

![Formula IIa](image)

or IIb

![Formula IIb](image)
in which \( R_1, R_2, n \) and \( m \) have the previously mentioned meanings, and \( A \) represents a halogen atom or a good "starting group" selected from among tosyloxy or mesyloxy, with a compound of the general formula III

\[
III
\]

in which \( X, Y, Z \) and \( W \) have the previously mentioned meanings.

The reaction is performed in the presence of a suitable solvent, for example, dimethylsulfoxide, dimethylformamide, alcohols, hydrocarbons, aromatic or not, ethers, such as dioxane or diphenyl ether, or mixtures of these solvents. This reaction is advantageously conducted in the presence of a base such as hydroxides, carbonates or bicarbonates of alkali metals, or even a mixture of these bases. It is possible to employ also hydrides of alkali metals. The most suitable temperatures vary between room temperature and reflux temperature of the solvent, and the reaction time is comprised of between 1 hour and 24 hours.

Method B.- By reaction of a compound of the general formula IIa, in which \( A \) represents an \(-\text{NH}_2\) radical, with 2,5-dimethoxytetrahydrofuran.

The reaction is carried out in the presence of a suitable solvent, for example, acetic acid, water, alcohols, ketones or mixtures of these solvents. The most suitable temperatures vary between ambient temperature and the reflux temperature of the solvent, and the reaction time is comprised between some
minutes and 24 hours.

Method C.- By reaction of a compound of a general formula IV

in which $R_1$, $R_2$ and $n$ have the meanings indicated previously, with a compound of the general formula V

where $X$, $Y$, $Z$, $W$ and $m$ have the previously mentioned meanings, and $B$ represents a halogen atom, or a good "starting group" selected from among tosyloxy or mesyloxy.

The reaction is carried out in the presence of a suitable solvent, for example, dimethylsulfoxide, dimethylformamide, alcohols, hydrocarbons, aromatic or not, ethers, dioxane or diphenyl ether, or mixtures of these solvents. This reaction is advantageously conducted in the presence of a base such as hydroxides, carbonates or bicarbonates of alkali metals, or even a mixture of these bases. The most suitable temperatures vary between room temperature and the reflux temperature of the solvent, and the reaction time is comprised of between 1 hour and 24 hours.
In the following examples the preparation of novel derivatives according to the invention is indicated. The examples below, given purely by way of illustration, must not however in any case, be taken as limiting the scope of the invention.

DESCRIPTION OF PREFERRED EMBODIMENTS

Method A

1. Preparation of 1-(2-Ethoxyethyl)-2-4-[4-(4-bromopyrazol-1-yl)butyl]piperazin-1-yl-methyl benzimidazole.

a) 1-(2-Ethoxyethyl)-2-(8-methylaza-5-azoniaspiro [4,5] decane) benzimidazole bromide.

A mixture of 1.5 g (5.21 mmoles) of 1-(2-Ethoxyethyl)-2-(1-piperzinyl)benzimidazole, 1.41 g (6.5 mmoles) of 1,4-dibromobutane and 0.72 g (5.2 mmoles) of potassium carbonate in 50 ml of chloroform is placed under reflux for 16 hours. It was cooled, filtered and evaporated. The residue was triturated in ethyl ether and 2.1 g of 1-(2-Ethoxyethyl)-2-(8-methylaza-5-azoniaspiro [4,5] decane benzimidazole bromide was obtained, a hygroscopic solid which is used as such, without further purification.

1H-NMR (CDCl3): 1.05 (t,3H); 2.25 (m,4H); 3.25-4.15 (m,18H); 4.45 (t,2H); 7.27 (m,3H); 7.60 (m,1H).

b) 1-(2-Ethoxyethyl)-2-4-[4-(4-bromopyrazol-1-yl)butyl]piperazin-1-yl-methyl benzimidazole.

Under reflux, for 12 hours, a mixture of 2.3 g (5.44 mmoles) of 1-(2-Ethoxyethyl)-2-(8-methylaza-5-azoniaspiro [4,5] decane) benzimidazole bromide, 0.92 g (6.28 mmoles) of 4-bromo-1-H-pyrazole, 1.38 g (0.01
mole) of potassium carbonate and 30 ml of dimethylformamide were heated under reflux for 12 hours. It was cooled, filtered and the filtrate evaporated to dryness. The residue was taken up again with chloroform and it was washed with water. The organic phase was dried with Na$_2$SO$_4$, it was filtered and evaporated. The resulting oil was purified on a chromatographic silica column (eluant: chloroform-methanol 95:5). In this way 0.78 g of the compound was obtained in liquid form.

The spectroscopic data for its identification are shown in Tables 1 and 2.

Example 2.- Preparation of 1-(2-Ethoxyethyl)-2-4-4-(4-bromopyrazol-1-yl)butyl]piperazinyl benzimidazole.

a) 1-(2-Ethoxyethyl)-2-(8-aza-5-azoniaspiro [4.5] decane)benzimidazole bromide.

The preparation is carried with the same procedure as that explained in example 1a.

$^1$H-NMR (CDCl$_3$): 1.08 (t, 3H); 2.37 (m, 4H); 3.42 (q, 2H); 3.7-4.15 (m, 14H); 4.32 (t, 2H); 7.27 (m, 3H); 7.60 (m, 1H).

b) 1-(2-Ethoxyethyl)-2-4-[4-(bromopyrazol-1-yl)butyl]piperazinyl benzimidazole.

The preparation was carried out with the same method as example 1b.

The salt with maleic acid was prepared in ethanol and its melting point was 137-139°C.

The spectroscopic data for its identification are shown in Tables 1 and 2.

Example 3.- Preparation of 1-(2-Ethoxyethyl)-2-4-[4-(imidazol-1-yl)butyl]piperazin-1-yl-methyl benzimidazole.
The preparation is carried out in a manner quite similar to that explained for examples la and lb. The spectroscopic data for its identification are given in Tables 1 and 2.

Example 4. - Preparation of 1-(2-Ethoxyethyl)-2-4-[4-(1,2,4-triazol-1-yl)butyl]piperazin-1-ylmethyl benzimidazole.

The preparation is carried out in a way quite similar to that explained in examples la and lb. The spectroscopic data for its identification are disclosed in Tables 1 and 2.

Example 5. - Preparation of 1-(2-Ethoxyethyl)-2-4-[4-(4-sulfopyrazol-1-yl)butyl]piperazin-1-ylmethyl benzimidazole.

The preparation is carried out in a manner quite similar to that explained in examples la and lb. The spectroscopic data for its identification are shown in Tables 1 and 2.

Example 6. - Preparation of 1-(2-Ethoxyethyl)-2-4-[4-(4-carboxypyrazol-1-yl)butyl]piperazin-1-ylmethyl benzimidazole.

According to the preparation explained in example la and lb the 1-(2-Ethoxyethyl)-2-4-[4-(4-ethyloxycarbonylpyrazol-1-yl)butyl]piperazin-1-ylmethyl benzimidazole was obtained crude; it was purified on a chromatographic silica column (eluant: chloroform-methanol 95:5).

$^1$H-NMR (CDCl$_3$): 1.12 (t, 3H); 1.45 (m, 5H); 1.90 (m, 2H); 2.44 (m, 10H); 3.41 (q, 2H); 3.60-3.86 (m, 4H); 4.0-4.3 (m, 4H); 4.50 (t, 2H); 7.28 (m, 3H); 7.75 (m, 1H); 7.8 (s, 2H). IR (film): 1715, 1560, 1470, 1225, 1120, 1040, 750 cm$^{-1}$
The salt with maleic acid was prepared in ethanol and its melting point was 114-117°C.

The preceding ester as prepared was hydrolysed by treatment with a solution in ethanol, for 3 hours at ambient temperature, with 10% caustic soda. The alcohol is evaporated and the aqueous solution is neutralised with acetic acid. It was evaporated to dryness and the acid was extracted from the residue by digestion with dichloromethane.

In this way the corresponding acid was obtained, of which the spectroscopic data for its identification are shown in Tables 1 and 2.

Example 7. - Preparation of 1-(2-Ethoxyethyl)-2-4-[4-(pyrazol-1-yl)butyl]piperazin-1-yl-methyl benzimidazole.

The preparation was carried out in a manner quite similar to that explained in examples la and lb.

The salt with maleic acid was prepared in ethanol and melted at 112-116°C.

The spectroscopic data for its identification are shown in Tables 1 and 2.

Example 9. - Preparation of 1-(2-Ethyxyethyl)-2-4-[4-(4-carboxypryazol-1-yl)butyl]piperazin-1-yl benzimidazole.

According the preparation explained in examples 2a and 2b 1-(2-Ethoxyethyl)-2-4-[4-(4-ethyloxycarbonylpyrazol-1-yl)butyl]piperazin-1-yl benzimidazole was obtained crude, this was purified on a chromatographic column of silica (eluant:chloroform-methanol 95:5).

$^1$H-NMR (CDCl$_3$): 1.1 (t,3H); 1.3 (t,3H); 1.8 (m,4H); 2.15-2.7 (m,6H); 3.25 (m,6H); 3.7 (t,2H); 3.8-4.3 (m,6H); 7.2 (m,3H); 7.5 (m,1H); 7.8 (s,2H).

IR (KBr): 2950, 1715, 1220, 1125, 760 cm$^{-1}$
The previously prepared ester was hydrolysed by treatment with 10% caustic soda for 15 hours at room temperature, of a solution in ethanol. The alcohol was evaporated and the aqueous solution was neutralised with hydrochloric acid. It was evaporated to dryness and the acid was extracted from the residue by digestion with chloroform.

In this way the corresponding acid was obtained which was triturated with ethyl ether. The compound crystallizes in this solvent with a melting point of 145-150°C.

The spectroscopic data for its identification are given in Tables 1 and 2.


The preparation was carried out in a manner quite similar to that explained in examples 1a and 1b.

The salt with fumaric acid was prepared in ethanol and melted at 123-130°C.

The spectroscopic datas for its identification are shown in Tables 1 and 2.

Method B

Example 8. Preparation of 1-(2-Ethoxyethyl)-2-{4-[4-(pyrrol-1-yl)butyl] piperazin-1-yl-methyl benzimidazole.

There was put under reflux for 3 hours a mixture of 6.4 g (22 mmoles) of 1-(2-Ethoxyethyl)-2-(1-methylpiperazinyl)benzimidazole, 6.25 g (22 mmoles) of N-(4-bromobutyl) phthalimide, 4.55 g (33 mmoles) of potassium carbonate and 4.62 g (30 mmoles) of sodium iodide in 100 ml of methyl ethyl ketone. It was cooled, filtered and the filtrate evaporated to dryness. The residue is taken up again with chloroform and with water. The organic base was dried with
Na$_2$SO$_4$, it was filtered and evaporated under vacuum. The resulting oil was purified on a chromatographic silica column (eluant: chloroform:methanol 95:5). In this way there were obtained 8.47 g of 1-(2-Ethoxyethyl)-2-4-(4-N-phthalimido-butyl)piperazin-1-yl-methyl benzimidazole.

$^1$H-NMR (CDCl$_3$): 1.1 (t,3H); 2.6 (m,4H); 2.45 (m,10H); 3.3 (q,2H); 3.5-3.8 (m,6H); 4.4 (t,2H); 7.15 (m,4H); 7.55 (m,4H).

Under reflux for 2 hours were heated a solution of 8.46 g (17.3 mmoles) of the compound previously obtained at 1.73 g (34.6 mmoles) of hydrazine hydrate in 150 ml of ethanol. It was cooled, filtered, washed with ethanol and the filtrate evaporated to dryness under vacuum. The residue was taken up with chloroform and washed with water, and dried, evaporated and 4.35 g of 1-(2-Ethoxyethyl)-2-4-(4-aminobutyl)piperazin-1-yl-methyl benzimidazole obtained which were used in another purification.

$^1$H-NMR (CDCl$_3$): 1.1 (t,3H); 1.45 (m,4H); 1.75 (s,2H); 2.05-2.75 (m,12H); 3.35 (q,2H); 3.6-3.9 (m,4H); 4.45 (t,2H); 7.20 (m,3H); 7.6 (m,1H).

b) 1-(2-Ethoxyethyl)-2-4-(4-(pyrrol-1-yl)butyl)piperazin-1-ylmethyl benzimidazole.

Under reflux, for 20 minutes, there was heated a solution of 2 g (5.57 mmoles) of 1-(2-Ethoxyethyl)-2-4-(4-aminobutyl)piperazin-1-yl-methyl benzimidazole and 0.735 g (5.57 mmoles) of 2,5-dimethoxytetrahydrofuran in 20 ml of acetic acid, poured over ice water, neutralized with Na$_2$HCO$_3$ and extracted with chloroform. It was dried with Na$_2$SO$_4$, and evaporated under vacuum to dryness. In this way 2.75 g of the crude compound was obtained which was purified on a Chromatographic silica column (eluant: chloroform:methanol 94:6).
The salt with fumaric acid was prepared in ethanol-ethyl ether, with a melting point of 138-142°C.

The spectroscopic data for its identification are given in Tables 1 and 2.

Method C

Example 6.- Preparation of 1-(2-Ethoxyethyl)-2-4-[4-(4-carboxypyrrozol-1-yl)butyl]piperazin-1-yl-methyl benzimidazole.

There was placed under reflux for 4 hours a mixture of 5 g (17.36 mmoles) of 1-(2-Ethoxyethyl)-2-(1-methylpiperazinyl) benzimidazole, 4.77 g (17.36 mmoles) of 1-(4-bromobutyl)-4-pyrazole of ethyl carboxylate, 3.52 g (26 mmoles of potassium carbonate and 3.52 g (23.5 mmoles) of sodium iodide in 100 ml of methyl ethyl ketone. It was cooled, filtered and the filtrate evaporated to dryness. The residue was taken up again with chloroform and with water, the organic phase with Na₂SO₄, it was filtered and evaporated under vacuum. The resultant crude product was purified on a chromatographic silica column (eluant: chloroform-methanol 95:5) and in this way 4.85 g of 1-(2-Ethoxyethyl)-2-4-[4-(4-ethyloxycarbonylpyrazol-1-yl)butyl]piperazin-1-yl-methyl benzimidazole was obtained.

The spectroscopic data of the compound are the same already given in example 6 of method A.

This ester was hydrolysed similarly to the method explained in example 6 of method A and the acid obtained with the spectroscopic data explained in Tables 1 of 2.

The preparation is carried out in a manner quite similar to that explained in the preceding example, and the compound of salt with fumaric acid has a melting point of 137-142°C was obtained.

The spectroscopic data for its identification was explained in Tables 1 and 2.

Pharmacological Activity

The products according to the present invention are powerful antihistaminics and are characterized by the fact that they are free from sedative effects, contrary to the majority of the known antihistaminics.

"In vivo" Antihistaminic Activity

The antihistaminic activity was studied by determining the protection in the face of the mortality induced by the product 48/80 in the rat. This test was realized in accordance with the technique described by C.J.E. Niemegeers and cols. (Arch. int. Pharmacodyn. 234, 164-176 (1978).
<table>
<thead>
<tr>
<th>Example n°</th>
<th>R₁</th>
<th>R₂</th>
<th>n</th>
<th>m</th>
<th>R</th>
<th>Méthode</th>
<th>IR (cm⁻¹) (film)</th>
</tr>
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<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>1</td>
<td>4</td>
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<td>A</td>
<td>2937, 2808, 1465, 1117, 952, 747</td>
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<td>A</td>
<td>maleate (KBr): 2975, 2881, 1706, 1619, 1475, 1356, 862, 744, 650</td>
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<tr>
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<td>H</td>
<td>1</td>
<td>4</td>
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<td>2938, 2812, 1463, 1132, 749, 665</td>
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<tr>
<td>4</td>
<td>H</td>
<td>H</td>
<td>1</td>
<td>4</td>
<td><img src="image4" alt="Residue" /></td>
<td>A</td>
<td>2940, 2812, 1673, 1463, 1332, 1136, 1011, 749</td>
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<td>H</td>
<td>1</td>
<td>4</td>
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<td>A</td>
<td>3600-2800, 1662, 1464, 1220, 1183, 1129, 1052, 670</td>
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<td>H</td>
<td>H</td>
<td>1</td>
<td>4</td>
<td><img src="image6" alt="Residue" /></td>
<td>A/C</td>
<td>3600-3200, 2931, 1706, 1462, 1119, 756</td>
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<td>H</td>
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<td>4</td>
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<td>2838, 2825, 1512, 1462, 1125, 913, 731</td>
</tr>
<tr>
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<td>H</td>
<td>H</td>
<td>1</td>
<td>4</td>
<td><img src="image8" alt="Residue" /></td>
<td>B/C</td>
<td>2970, 1643, 1463, 1416, 1332, 1120, 749</td>
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<tr>
<td>9</td>
<td>H</td>
<td>H</td>
<td>0</td>
<td>4</td>
<td><img src="image9" alt="Residue" /></td>
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<td>3360-3150, 2944, 1700, 1525, 1469, 1412, 1125, 750</td>
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### TABLEAU 2

<table>
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<tr>
<th>Example n°</th>
<th>$^1$H-RMN (CDCl$_3$)</th>
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<tr>
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<td>1.12 (t, 3H); 1.46 (m, 2H); 1.81 (m, 2H); 2.45 (m, 10H); 3.41 (q, 2H); 3.81 (m, 4H); 4.08 (t, 2H); 4.50 (t, 2H); 7.33 (m, 5H); 7.69 (m, 1H)</td>
</tr>
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<td>1.13 (t, 3H); 1.60 (m, 2H); 1.87 (m, 2H); 2.55 (t, 2H); 2.76 (m, 4H); 3.44 (m, 6H); 3.81 (t, 2H); 4.12 (dt, 4H); 7.12-7.61 (m, 6H)</td>
</tr>
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<td>1.12 (t, 3H); 1.70 (m, 4H); 2.35 (m, 10H); 3.40 (q, 2H); 3.75 (m, 6H); 4.35 (t, 2H); 6.9 (s, 1H); 7.0 (s, 1H); 7.18-7.45 (m, 4H); 7.7 (m, 1H)</td>
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<td>4</td>
<td>1.13 (t, 3H); 1.46 (m, 2H); 1.90 (m, 2H); 2.45 (m, 10H); 3.42 (q, 2H); 3.76 (t, 2H); 3.88 (s, 2H); 4.20 (t, 2H); 4.52 (t, 2H); 7.30 (m, 3H); 7.71 (m, 1H); 7.94 (s, 1H); 8.06 (s, 1H)</td>
</tr>
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<td>$^d$-DMSO 1.0 (t, 3H); 2.11 (m, 4H); 3.67 (m, 16H); 4.37 (t, 2H); 4.65 (t, 2H); 7.7 (m, 6H)</td>
</tr>
<tr>
<td>6</td>
<td>1.10 (t, 3H); 1.58 (m, 2H); 1.86 (m, 2H); 2.68 (m, 10H); 3.38 (q, 2H); 3.73 (t, 2H); 3.89 (s, 2H); 4.15 (t, 2H); 4.48 (t, 2H); 7.27 (m, 3H); 7.84 (m, 3H)</td>
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<td>1.12 (t, 3H); 1.50 (m, 2H); 1.85 (m, 2H); 2.45 (m, 10H); 3.41 (q, 2H); 3.75 (t, 2H); 3.87 (s, 2H); 4.14 (t, 2H); 4.50 (t, 2H); 6.22 (m, 1H); 7.19-7.47 (m, 6H)</td>
</tr>
<tr>
<td>8</td>
<td>1.1 (t, 3H); 1.70 (m, 4H); 2.69 (m, 10H); 3.40 (q, 2H); 3.55-3.90 (m, 6H); 4.46 (t, 2H); 6.12 (m, 2H); 6.62 (m, 2H); 7.1-7.7 (m, 4H)</td>
</tr>
<tr>
<td>9</td>
<td>1.14 (t, 3H); 1.59 (m, 2H); 1.90 (m, 2H); 2.4-2.8 (m, 6H); 3.3-3.6 (m, 6H); 3.83 (t, 2H); 4.17 (dt, 4H)</td>
</tr>
<tr>
<td>10</td>
<td>1.12 (t, 3H); 1.55 (m, 2H); 1.80 (m, 2H); 2.1-2.6 (m, 10H); 3.41 (q, 2H); 3.86 (m, 6H); 4.49 (t, 2H); 7.29 (m, 4H); 7.75 (m, 1H)</td>
</tr>
</tbody>
</table>
The products according to the present invention are administered i.p. to rats. After 60 minutes the compound 48/80 is administered (0.5 mg/kg, i.v.). The protective activity is defined as the survival of the rats 4 hours after the i.v. injection of 48/80.

The activity of the products at several doses in order to determine the dose capable of protecting 50% of the animals (ED-50) was studied.

Then the antihistaminic activity of several of the products according to the present patent application are summarized. This activity is compared with that of difenhidramine, a reference antihistaminic agent. The majority of the products according to the present invention are much more active than difenhidramine, considering that their ED-50 is much smaller.

"In vivo" Antihistaminic Activity:
Protection from death induced by 48/80

<table>
<thead>
<tr>
<th>Example no.</th>
<th>ED-50 (mg/kg, i.p.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.09</td>
</tr>
<tr>
<td>2</td>
<td>2.7</td>
</tr>
<tr>
<td>3</td>
<td>0.13</td>
</tr>
<tr>
<td>4</td>
<td>0.036</td>
</tr>
<tr>
<td>5</td>
<td>2.6</td>
</tr>
<tr>
<td>6</td>
<td>0.064</td>
</tr>
<tr>
<td>7</td>
<td>0.02</td>
</tr>
<tr>
<td>8</td>
<td>0.02</td>
</tr>
<tr>
<td>9</td>
<td>0.84</td>
</tr>
<tr>
<td>10</td>
<td>0.66</td>
</tr>
<tr>
<td>Difenhidramine</td>
<td>0.84</td>
</tr>
</tbody>
</table>
Sedative Effect: 1) Irwin Test

To study the sedative effect of the products according to the present invention, they are administered to rats i.p. and the behavior of the animals is observed, following the standards described in the test of S. Irwin (Science, 136, 123-128 (1962)).

The results obtained in the two evaluations which reflect the sedative action are collected below:

- Pas.: Passivity, sedation, prostration. Quantitative evaluation between 0 and 3. They were performed 1, 2 and 3 hours after the treatment.

- Atax.: Ataxia, the alterations in coordination in locomotion were evaluated. They were evaluated between 0 and 3. They were performed 1, 2 and 3 hours after the treatment.

Below are summarized the results of the study of the sedative action of some of the products according to the present invention, by way of example. This activity was compared with that of difenhidramine, reference antihistamine. The products according to the present invention have shown very slight sedative action, contrary to difenhidramine which is established to be toxic at the dose of 80 mg/kg, i.p., on account of CNS depressor effects.
Sedative Effect: 1) Irwin Test

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Dose (mg/kg)</th>
<th>Effect</th>
<th>Pas.</th>
<th>Atax.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(80)</td>
<td>1.4</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(40)</td>
<td>0</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(80)</td>
<td>0.7</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(80)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(80)</td>
<td>0.4</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(80)</td>
<td>0.4</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(80)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(80)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>(160)</td>
<td>0</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>(80)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>(80)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Difenhidramine</td>
<td>(40)</td>
<td>0</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(80)</td>
<td></td>
<td>Toxic</td>
<td></td>
</tr>
</tbody>
</table>

Sedative Effect: 2) Potentiation of the sleep time induced by pentobarbital.

Study of the potentiation of the sleep time due to pentobarbital was carried out by following the method described by L.E. Allen and cols. (Arz. Forsch. 24, (6), (1974)). The products studied were administered orally. One hour later the sodium pentobarbital was administered (35 mg/kg, s.c.) and the time the animals are delayed in waking up is determined. The sleep time was compared with a group of control animals, treated only with sodium pentobarbital.

In order to complete the studies which
demonstrate the absence of sedative action of the products according to the present invention, in this test the activity of one of the most powerful products was compared with a lesser sedative effect (example 7) with the reference antihistamine, difenhidramine. Below are given the results of this test with example 7 and difenhidramine. It is obvious that difenhidramine potentiates significantly the sleep time at the dose of 20 mg/kg, whilst example 7 does not potentiate the sleep time induced by pentobarbital even at 320 mg/kg, the maximum dose tested.

**Sedative Effect: 2) Potentiation of the sleep time induced by pentobarbital**

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Dose (mg/kg, orally)</th>
<th>Potentiation of sleep time</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>80</td>
<td>10% N.S.</td>
</tr>
<tr>
<td>20</td>
<td>160</td>
<td>11% N.S.</td>
</tr>
<tr>
<td>320</td>
<td></td>
<td>22% N.S.</td>
</tr>
</tbody>
</table>

Difenhidramine

| 10  | 22% N.S. |
| 20  | 38% *    |

N.S.: Not significant

* : Significant difference with the control group (p < 0.05)

Below will be indicated by way of example, a particular galenic form of the derivatives according to present invention.
## Tablets

### Formula per Tablet

<table>
<thead>
<tr>
<th></th>
<th>Grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example No. 7</td>
<td>10.00 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>54.00 mg</td>
</tr>
<tr>
<td>Cornstarch</td>
<td>26.00 mg</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>18.00 mg</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone</td>
<td>6.00 mg</td>
</tr>
<tr>
<td>Sodium croscarmellose</td>
<td>3.60 mg</td>
</tr>
<tr>
<td>Colloidal sillicic dioxide</td>
<td>0.60 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.20 mg</td>
</tr>
</tbody>
</table>
The claims defining the invention are as follows:

1. Novel compounds derived from benzimidazole characterized in that they correspond to the general formula I, and their therapeutically acceptable salts,

\[
\text{I} \quad \text{CH}_4\text{CH}_2\text{OCH}_2\text{CH}_3
\]

in which:
- \( R_1 \) and \( R_2 \), equal or different, represent a hydrogen atom, a halogen, a lower alkyl radical, a hydroxy radical, an alkoxy radical, an alkyl carboxylate radical, an aryl or substituted aryl radical,
- \( n \) can have the values 0 or 1,
- \( m \) can have the values 2 to 4,
- \( X, Y, Z \) and \( W \) are equal or different, and even form part of the same ring, aromatic or not, represent a nitrogen atom or a carbon atom bonded to a hydrogen atom, to a halogen or to another alkyl, aryl, carboxyalkyl, carboxylic, hydroxyl, alkylhydroxy, sulfonic, or alkylsulfonic radical.
2. The compounds corresponding to the general formula I according to claim 1, selected from the following group:

- 1-(2-Ethoxyethyl)-2-{4-[4-(4-bromopyrazol-1-yl)butyl]piperazin-1-yl-methyl}benzimidazole.
- 1-(2-Ethoxyethyl)-2-{4-[4-(4-bromopyrazol-1-yl)butyl]piperazinyl}benzimidazole.
- 1-(2-Ethoxyethyl)-2-{4-[4-(imidazol-1-yl)butyl]pipérizinyl}benzimidazole.
- 1-(2-Ethoxyethyl)-2-{4-[4-(1,2,4-triazol1-yl)butyl]pipérizinyl}benzimidazole.
- 1-(2-Ethoxyethyl)-2-{4-[4-(4-sulfopyrazol-1-yl)butyl]pipérizinyl}benzimidazole.
- 1-(2-Ethoxyethyl)-2-{4-[4-(4-carboxypyrazol-1-yl)butyl]pipérizinyl}benzimidazole.
- 1-(2-Ethoxyethyl)-2-{4-[4-(4-thyloxycarbonylpyrazol-1-yl)butyl]pipérizinyl}benzimidazole.
- 1-(2-Ethoxyethyl)-2-{4-[4-(pyrazol-1-yl)butyl]pipérizinyl}benzimidazole.
- 1-(2-Ethoxyethyl)-2-{4-[4-(pyrrol-1-yl)butyl]pipérizinyl}benzimidazole.
- 1-(2-Ethoxyethyl)-2-{4-[4-(4-carboxypyrazol-1-yl)butyl]benzimidazole.
- 1-(2-Ethoxyethyl)-2-{4-[4-(4-thyloxycarbonylpyrazol-1-yl)butyl]benzimidazole.
- 1-(2-Ethoxyethyl)-2-{4-[4-(4,5-dichloroimidazol-1-yl)butyl]pipérizinyl}benzimidazole.
3. Process for the preparation of compounds according to one of claims 1 and 2, characterized by the practicing of at least one of the following operations:

3a- By reaction of a compound of the general formula IIa

$$\text{IIa}$$

$$\begin{align*}
R_1 & \quad \text{(CH}_2\text{)}_n \quad N \quad \text{IIa}
R_2 & \quad \text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3
\end{align*}$$

or IIb

$$\text{IIb}$$

$$\begin{align*}
R_1 & \quad \text{(CH}_2\text{)}_n \quad N \quad \text{IIb}
R_2 & \quad \text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3
\end{align*}$$

in which $$R_1$$, $$R_2$$, n and m have the previously mentioned meanings, and A represents a halogen atom, or a good "starting group" selected from among tosylxy or mesyloxy, with a compound of general formula III

$$\text{III}$$

in which X, Y, Z, and W have the previously mentioned meanings.
3b- By reaction of a compound of the general formula IIa, in which A represents a \(-\text{NH}_2\) radical, with 2,5-dimethoxytetrahydrofuran.

3c- By reaction of a compound of the general formula IV

![Formula IV](attachment:image)

in which R1, R2 and n have the previously mentioned meanings, with a compound of general formula V

![Formula V](attachment:image)

where X, Y, Z, W and m have the previously mentioned meanings and B represents a halogen atom or a good "starting group" selected from among tosylxy or mesyloxy.
4. By way of medicaments, the derivatives of the general formula I and their therapeutically acceptable salts, according to claims 1 and 2, in particular as medicaments used as antihistamines.

5. Pharmaceutical compositions, characterized by the fact that they contain, besides a pharmaceutically acceptable support, at least one derivative of the general formula I or one of its physiologically acceptable salts, according to one of claims 1 and 2.

6. Method of practising prophylaxis and of treating various allergic disorders caused by histamine, utilizing a derivative of the general formula I and its physiologically acceptable salts, according to one of claims 1 and 2.

Dated: 24 July 1991

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NOVEL DERIVATIVES OF BENZIMIDAZOLE, THEIR
PREPARATION, AND THEIR USE AS MEDICAMENTS

DESCRIPTIVE ABSTRACT

The present invention relates to novel compounds
derived from benzimidazole, characterized in that they
correspond to the general formula I, and their
therapeutically acceptable salts,

\[ \text{R}_1 \text{CHCHOCH}_2 \text{R}_2 \]

in which:

- \( \text{R}_1 \) and \( \text{R}_2 \), equal or different, represent a
  hydrogen atom, a halogen, a lower alkyl radical, a
  hydroxy radical, an alkoxy radical, an alkyl
  carboxylate radical, an aryl or substituted aryl
  radical,

- \( n \) may have the values 0 or 1,

- \( m \) may have the values 2 to 4,

- \( X, Y, Z \) and \( W \), equal or different, and even
  forming part of another ring, aromatic or not,
  represents a nitrogen atom or a carbon atom bonded to
  a hydrogen atom, a halogen or another alkyl, aryl,
  carboxyalkyl, carboxylic, hydroxyle, alkylhydroxy,
  sulfonic and alkylsulfonic radical. The present
  invention relates also to the process of preparing
  compounds for these purposes, and their use for the
  manufacture of medicaments intended for prophylaxis
  and for the treatment of various allergic disorders
  caused by histamine.