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(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIP (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
- of inventorship (Rule 4.17(iv)) for US only

Published:
- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MONOHYDRATE HYDROCHLORIDE OF THE 4-HYDROXYCARBAMOYL-PHENYL-)CARBAMIC ACID (6-DIETHYLAMINOMETHYL-NAPHTALEN-2-YL) ESTER

(57) Abstract: A compound having formula (I) and a process for the preparation thereof are described.

![Chemical Structure](image)
"MONOHYDRATE HYDROCHLORIDE OF THE 4-
HYDROXYCARBAMOYL-PHENYL)-CARBAMIC ACID (6-
DIETHYLAMINOMETHYL-NAPHTALEN-2-YL) ESTER"

The present invention relates to a derivative of hydroxamic acid having anti-inflammatory activity.

PRIOR ART

Hydrochloride of (6-diethylaminomethyl-naphthalen-2-yl)-methyl ester of (4-hydroxycarbamoylphenyl)-carbamic acid (II)

\[
\text{II}
\]

has been described in US patent 6,034,096 as a derivative of hydroxamic acid having anti-inflammatory and immunosuppressive activity, probably owing to the ability thereof to inhibit the production of pro-inflammatory cytokines. This compound is obtained according to Example 12 of the above-mentioned patent as an anhydrous, amorphous, hygroscopic, deliquescent solid which is difficult to handle.

STATEMENT OF INVENTION

The subject-matter of the present invention is the crystalline form of monohydrous hydrochloride of (6-diethylaminomethyl-naphthalen-2-yl)-methyl ester of (4-hydroxycarbamoylphenyl)-carbamic acid (I).
This form is particularly advantageous from the industrial perspective because it is stable and simpler to handle than the anhydrous and amorphous form described above.

The monohydrate (I) is obtained by means of a process which comprises the following steps:

a) reaction of 4-(6-diethylaminomethyl-naphthalen-2-ylmethoxycarbonylamino)benzoic acid with thionyl chloride in tetrahydrofuran as the solvent to provide the corresponding acid chloride;

b) reaction of the acid chloride with an aqueous solution of hydroxylamine in tetrahydrofuran as the solvent and precipitation of the hydrochloride by addition of hydrochloric acid;

c) dissolution of the hydrochloride obtained in the preceding step in a solution of sodium bicarbonate;

d) extraction of the solution with a mixture of tetrahydrofuran and ethyl acetate;

e) precipitation of the monohydrorous hydrochloride by addition of 37% HCl.

The presence of solvation water has been confirmed by means of DSC analysis, which shows a desolvation endotherm between 80 and 120°C (Figure 1), and by means of thermogravimetric analysis (Figure 2), which shows a loss of 3.3% between 40 and 120°C, owing to the loss of the crystallisation solvent. The crystalline form of the product is
confirmed by X-ray analysis (Figure 3).

The present invention further relates to pharmaceutical compositions containing compound (I); these compositions can be in the form of capsules, pills, coated pills, creams, ointments or vials for oral, intramuscular or intravenous administration.

The compound of formula (I) is contained alone or in admixture with conventional carriers or excipients, for example, those described in Remington’s Pharmaceutical Sciences Handbook, XVII ed., Mack Pub., N.Y., U.S.A.

The invention will now be explained below in greater detail with reference to the following Example.

EXAMPLE

Materials and methods

The differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) were carried out with a Mettler TA8000 instrument provided with a cell DSC821/700 and by a TG 50 thermobalance under the following conditions:

- gas: nitrogen 20–30 ml/min.;
- containers: open capsules of aluminium;
- heating rate: 10°C/min.;
- evaluation of the thermal events by means of “Star System” software.

The 4-(6-diethylaminomethyl-naphthalen-2-ylmethoxycarbonylamino)-benzoic acid can be prepared as described in Example 12, point C, of US 6,034,096.

The acid (1.22 kg, 3 moles) was suspended in THF (19 l) and the mixture was agitated under nitrogen over night at ambient temperature. The mixture was then cooled to 0°C and thionyl chloride (0.657 l, 9
moles) was added slowly, still under nitrogen, with the temperature being maintained below 10°C. The reaction mixture was heated under reflux for 60 minutes, DMF (26 ml) was added and the mixture was further heated under reflux for 60 minutes.

The solvent was evaporated under vacuum, toluene was added to the residue and was then evaporated. This operation was repeated twice, then the residue was suspended in THF (11.5 l) and the mixture was cooled to 0°C.

The mixture was then poured into a cold solution of hydroxylamine (50% aq., 1.6 l, 264 moles) in 5.7 l of water. The mixture was then cooled to ambient temperature and agitated for 30 minutes. 6M HCl was added until pH 2 was reached and the mixture was partially evaporated under vacuum in order to eliminate most of the THF. The solid was filtered, washed repeatedly with water and dissolved in a solution of sodium bicarbonate (2.5%, 12.2 l). The solution was extracted with 18.6 l of a mixture of THF and ethyl acetate (2:1 v/v). 37% HCl (130 ml) were added to the organic layer in order to precipitate the monohydrate of the (6-diethylaminomethyl-naphthalen-2-yl)-methyl ester hydrochloride of the (4-hydroxycarbamoyl-phenyl)-carbamic acid. If necessary, this operation can be repeated several times to remove any residues of the original acid.

Finally, the solid was dried under vacuum (approximately 30 mbar, 50°C), producing 0.85 kg (60%) of compound (I).

HPLC purity: 99.5%; water content (Karl Fischer method): 3.8%; (argentometric) assay: 99.8%.
Elemental analysis  
C%   H%   Cl%   N%

Calculated for  
C_{24}H_{30}ClN_{5}O_{5}  
60.56   6.35   7.45   8.83

Found  
61.06   6.48   7.48   8.90

DESCRIPTION OF THE FIGURES

Figure 1:  DSC analysis of compound (I)
Figure 2:  thermogravimetric analysis of two samples of compound (I)
Figure 3:  diffractometric analysis of compound (I) unmodified and after drying.
CLAIMS

1. Monohydrate hydrochloride of (6-diethylaminomethyl-naphthalen-2-yl)-methyl ester of (4-hydroxycarbamoylphenyl)-carbamic acid of formula (I)

\[
\begin{align*}
\text{NH} & + \text{Cl}^- \\
\text{NH} & \text{O} \text{N} \text{HOS} + \text{H}_2\text{O}
\end{align*}
\]

in crystalline form.

2. Compound according to claim 1, characterised by the diffraction spectrum shown in Figure 3.

3. Pharmaceutical compositions containing the compound of claim 1 or 2.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C271/28 A61K31/325 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<tr>
<td>A</td>
<td>US 6 034 096 A (BERTOLINI GIORGIO ET AL) 7 March 2000 (2000-03-07) cited in the application the whole document</td>
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Date of the actual completion of the international search: 26 May 2004

Date of mailing of the international search report: 04/06/2004

Name and mailing address of the ISA


Authorized officer: Goetz, G
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<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 6034096 A</td>
<td>07-03-2000</td>
<td>IT MI60968 A1</td>
<td>14-11-1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 713300 B2</td>
<td>25-11-1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2896497 A</td>
<td>05-12-1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 9709234 A</td>
<td>10-08-1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69703207 D1</td>
<td>02-11-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69703207 T2</td>
<td>01-02-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 901465 T3</td>
<td>18-12-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 0901465 A1</td>
<td>17-03-1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GR 3035128 T3</td>
<td>30-04-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2000510472 T</td>
<td>15-08-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PL 329873 A1</td>
<td>12-04-1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SK 157998 A3</td>
<td>13-04-1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2254066 A1</td>
<td>20-11-1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1221403 A, B</td>
<td>30-06-1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CZ 9803667 A3</td>
<td>16-06-1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 9743251 A1</td>
<td>20-11-1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2151267 T3</td>
<td>16-12-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 2000010982 A</td>
<td>25-02-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 901465 T</td>
<td>31-01-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RU 2177473 C2</td>
<td>27-12-2001</td>
</tr>
</tbody>
</table>