(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 August 2006 (31.08.2006)

PCT

(10) International Publication Number
WO 2006/090263 A1

(51) International Patent Classification:
*C07D 211/32* (2006.01) *A61P 25/28* (2006.01)
*A61K 31/445* (2006.01)

(21) International Application Number:
PCT/IB2006/000416

(22) International Filing Date:
28 February 2006 (28.02.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
436/DEL/2005 28 February 2005 (28.02.2005) IN

(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; Plot No. 90, Sector - 32, Gurgaon, Haryana 122 001 (IN).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **NATH, Asok** [IN/IN]; House No. 680, Sector-14, Gurgaon, Haryana 122001 (IN). **PRASAD, Mohan** [IN/IN]; House No. P-3/3, Phase-II, Dlf Qutab Enclave, Gurgaon, Haryana 122001 (IN). **KUMAR, Yatendra** [IN/IN]; U-26/5, Phase-III, Dlf Qutab Enclave, Gurgaon, Haryana 122001 (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, 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, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**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.*

WO 2006/090263 A1

(54) Title: STABLE FORM I DONEPEZIL HYDROCHLORIDE AND PROCESS FOR ITS PREPARATION AND USE IN PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The present invention provides stable polymorphic Form I donepezil hydrochloride, processes for its preparation, use in pharmaceutical compositions and methods of treating Alzheimer's disease using the pharmaceutical compositions.

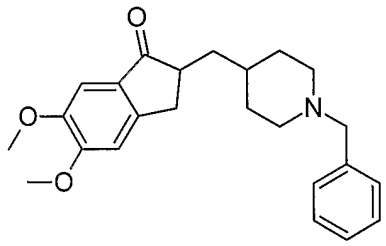
# STABLE FORM I DONEPEZIL HYDROCHLORIDE AND PROCESS FOR ITS PREPARATION AND USE IN PHARMACEUTICAL COMPOSITIONS

## Field of the Invention

The present invention provides stable polymorphic Form I donepezil hydrochloride, processes for its preparation, use in pharmaceutical compositions and methods of treating Alzheimer's disease using the pharmaceutical compositions.

## Background of the Invention

Donepezil is chemically, 2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dimethoxy indan-1-one of Formula I and is used in the treatment of mild to moderate dementia of Alzheimer's type. It is commercially available as its hydrochloride salt.



**FORMULA I**

Several processes have been reported for the preparation of donepezil or its salt (US 4,895,841; US 5,606,064; US 6,252,081; US 6,413,986; PCT Application WO 97/22584 and J. Med. Chem. 1995, 38 (24), 4821-4829). Our earlier application WO 04/086285 provides a process for preparing donepezil and its salts.

US 4,895,841 provides a process for preparing donepezil hydrochloride by crystallizing crude donepezil hydrochloride from a mixture of methanol and diisopropyl ether. Although no particular polymorphic form is mentioned in the specification of the '841 patent, it is believed that Form I of donepezil hydrochloride is obtained by employing such crystallization.

PCT Patent Application WO97/46527; WO 97/46526 and their equivalent US Patent Nos. 6,140,321 and 5,985,864 provide processes for preparing polymorphic forms I, II, III, IV and V of donepezil hydrochloride. In particular, Form I is prepared by heating

donepezil hydrochloride in methanol to get a solution which is then cooled under ice cooling and to it is added diethyl ether followed by filtration of the crystals to get Form I donepezil hydrochloride. The product so obtained was found to be sticky in nature.

US Application No 2004/0229914 provides a process for preparing crystalline Form VI of donepezil hydrochloride. PCT Application WO 04/092137 provides crystalline donepezil hydrochloride Form H1, Form H2, crystalline donepezil hydrochloride monohydrate and crystalline donepezil hydrochloride sesquihydrate. US 6,734,195 provides processes for making amorphous donepezil hydrochloride.

PCT Patent Application WO 99/29668 provides a process for making crystal A, B and C of donepezil. PCT Application WO 04/099142 provides the hydrobromide salt of donepezil. It further provides donepezil hydrobromide in solid state crystalline Forms I and II.

## Summary of the Invention

The present inventors have noticed that polymorphic Form I of donepezil hydrochloride when prepared as per the process reported in the prior art is not stable and has a tendency to convert to other polymorphic forms, especially Form III. It also was observed by the present inventors that after addition of ether to a solution of donepezil hydrochloride in methanol at a higher or ambient temperature, formation of Form I of donepezil is accompanied by contamination with Form III crystals if it takes more than forty five minutes to cool the resultant mass to less than 20°C. The so obtained Form I of donepezil hydrochloride, whenever stirred with water or any solvent at ambient temperature, converts to Form III at a much faster rate.

The present inventors have now obtained a stable polymorphic Form I donepezil hydrochloride having no or little tendency to convert to any other polymorphic form of donepezil hydrochloride.

Accordingly, in one general aspect there is provided a stable polymorphic Form I of donepezil hydrochloride. Embodiments of the stable polymorphic Form I of donepezil hydrochloride may include one or more of the following features. For example, the

donepezil hydrochloride may have no detectable quantity of other polymorphic forms of donepezil hydrochloride. The donepezil hydrochloride may have 2% or less of other polymorphic forms of donepezil hydrochloride. The donepezil hydrochloride may be incorporated into a dosage form with one or more pharmaceutically acceptable excipients. The donepezil hydrochloride may have the pattern illustrated in Figures 1 and/or 2.

In another general aspect there is provided a process for preparing stable Form I of donepezil hydrochloride. The process includes (a) adding an optionally pre-cooled anti-solvent to a solution of donepezil hydrochloride at 30°C or less; (b) rapidly cooling the resultant solution; and (c) isolating Form I of donepezil hydrochloride from the reaction mass thereof.

Embodiments of the process may include one or more of the following features. For example, the anti-solvent may be characterized by the donepezil hydrochloride being insoluble, practically insoluble or very slightly soluble in the anti-solvent. The anti-solvent may be diisopropyl ether or diethyl ether.

The solution of step (b) may be cooled to 25°C or less. The cooling may be effected in 30 minutes or less.

The donepezil hydrochloride may have no detectable quantity of other polymorphic forms of donepezil hydrochloride. The donepezil hydrochloride may have 2% or less of other polymorphic forms of donepezil hydrochloride.

In another general aspect there is provided a pharmaceutical composition that includes stable polymorphic Form I of donepezil hydrochloride and one or more pharmaceutically acceptable excipients and diluents. The donepezil hydrochloride has no tendency to convert to any other polymorphic form.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the donepezil hydrochloride may have no detectable quantity of other polymorphic forms of donepezil hydrochloride. The donepezil hydrochloride may have 2% or less of other polymorphic forms of donepezil hydrochloride.

In another general aspect there is provided a method of treating mild to moderate dementia of Alzheimer's type. The method includes administering to a mammal in need thereof a therapeutically effective amount of stable polymorphic Form I of donepezil hydrochloride having no tendency to convert to any other polymorphic form.

Embodiments of the method of treating may include one or more of the following features. For example, the therapeutically effective amount of donepezil hydrochloride may be in the form of a pharmaceutical composition that includes one or more pharmaceutically acceptable excipients and diluents. The donepezil hydrochloride may have no detectable quantity of other polymorphic forms of donepezil hydrochloride. The donepezil hydrochloride may have 2% or less of other polymorphic forms of donepezil hydrochloride.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description and claims.

## Background of the Invention

Figure 1 is an X-Ray Powder Diffraction Pattern of stable Form I donepezil hydrochloride

Figure 2 is a table of the two-theta values associated with the pattern of Figure 1.

## Detailed Description of the Invention

A first aspect of the present invention provides stable polymorphic Form I of donepezil hydrochloride having no tendency to convert to any other polymorphic form. The stable polymorphic Form I of donepezil hydrochloride of the present invention has 2% or less of other polymorphic forms of donepezil hydrochloride. More preferably the stable Form I of donepezil hydrochloride has no detectable quantity of any other known polymorphic form of donepezil hydrochloride. The X-Ray powdered Diffraction (XRPD) pattern and associated two-theta values of stable Form I of donepezil hydrochloride is provided in Figures 1 and 2 of the accompanied drawing. The stability study performed on stable Form I of donepezil hydrochloride suggests that it is stable for more than 2 years

under normal stability studies and for more than six months under accelerated stability studies.

It has been found that Form I donepezil hydrochloride is stable and there is no change in the related substance content of Form I stored at 40 ± 2°C at 75 ± 5% relative humidity. There was no indication of a chemical degradation of Form I donepezil hydrochloride produced according the present invention.

A second aspect of the present invention provides a process for preparing stable Form I donepezil hydrochloride. The process includes the steps of:

a) adding an optionally pre-cooled anti-solvent to a solution of donepezil hydrochloride at 30°C or less;

b) rapidly cooling the resultant solution; and

c) isolating Form I of donepezil hydrochloride from the reaction mass thereof.

Donepezil hydrochloride to be used as the starting material can be prepared by any process known in the literature. The so obtained donepezil hydrochloride then is dissolved in methanol by heating to reflux temperature. The resultant solution can be clarified to remove foreign particulate matter or treated with activated charcoal to remove coloring and other related impurities. The clear solution is cooled to a temperature of 30°C or less and an optionally pre-cooled anti-solvent is added to it. The anti-solvent is characterized by the fact that donepezil hydrochloride is insoluble, practically insoluble or very slightly soluble in the anti-solvent. The terms insoluble, practically insoluble and very slightly soluble have their ordinary meanings as defined in United States Pharmacopoeia 2002. Diisopropyl ether and diethyl ether are examples of anti-solvents that can be employed.

After adding the anti-solvent the resultant mixture is rapidly cooled to 25°C or less in less than 45 minutes and then maintained at 0 to 15°C for an hour or less. The separated crystals are filtered and dried to get stable polymorphic Form I of donepezil hydrochloride. The purity of Form I of donepezil so obtained is greater than 99.9% when determined by known High Performance Liquid Chromatography (HPLC) methods.

A third aspect of the present invention provides a pharmaceutical composition comprising as its active ingredient stable polymorphic Form I of donepezil hydrochloride having no tendency to convert to any other polymorphic form. With the active ingredient, the pharmaceutical composition includes one or more pharmaceutically acceptable excipients/diluents. The pharmaceutical composition of the present invention may be in the form of a solid or liquid dosage forms for oral, parenteral or topical use and may have immediate or sustained release characteristics. The dosage forms possible include tablets, capsules, powders, granules, creams, lotions, ointments, injectables, ophthalmic or otic solutions, suspensions, elixirs and the like.

A fourth aspect of the present invention provides a method of treating mild to moderate dementia of Alzheimer's type by administering to a mammal in need thereof a therapeutically effective amount of stable polymorphic Form I of donepezil hydrochloride having no tendency to convert to any other polymorphic form.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

## EXAMPLE 1

## PREPARATION OF CRUDE DONEPEZIL HYDROCHLORIDE

To a stirred mixture of 2,3-dihydro-5,6-dimethoxy-2-(4-piperidinyl)methyl-indan-1-one, hydrochloride (80 g), tetrabutyl ammonium bromide (8 g), potassium carbonate (72 g) in water (320 ml) and methylene chloride (400 ml) benzyl bromide (42.3 g) was added at ambient temperature. After addition, the reaction mixture was stirred at the same temperature. The organic layer was separated and stirred with water (160 ml) containing concentrated hydrochloric acid (51.2 ml) at ambient temperature. The organic layer was separated and concentrated under reduced pressure. The residue obtained was dissolved in water (800 ml) and extracted with ethyl acetate (400 ml). The organic layer was discarded and the pH of the aqueous layer was adjusted to 9.5 with aqueous ammonia solution. The aqueous solution then was extracted with ethyl acetate (800 ml). The ethyl acetate extract then was washed with water (2 x 600 ml). The organic layer was concentrated and the

residue dissolved in methanol (480 ml). Concentrated hydrochloric acid (38.4 g) was added to the solution. Diisopropyl ether (960 ml) then was added to the solution at 25°C. The solid that separated out on stirring at 5 to 10°C was filtered and dried to get crystals of donepezil hydrochloride.

Yield: 80 g.

HPLC Purity: 99.95%.

## EXAMPLE 2

## PREPARATION OF STABLE POLYMORPHIC FORM I OF DONEPEZIL HYDROCHLORIDE

A mixture of crude donepezil hydrochloride (70 gm) in methanol (490 ml) was heated to reflux to get a clear solution. The solution was cooled to 25°C and it diisopropyl ether (840 ml) was added to the cooled solution. The resulting mass was cooled to 10°C in less than 15 minutes and stirred at 5-10°C for the next 30 minutes. The separated solid was filtered and dried under reduced pressure followed by drying in air oven to get stable polymorphic Form I of donepezil hydrochloride.

Yield: 63 gm

HPLC Purity: More than 99.9%.

## EXAMPLE 3

## PREPARATION OF STABLE POLYMORPHIC FORM I OF DONEPEZIL HYDROCHLORIDE

A mixture of crude donepezil hydrochloride (10 gm) in methanol (70 ml) was heated to 65°C to get a clear solution. The clear solution was cooled to 10°C and diisopropyl ether (120 ml) was added to the cooled solution over 15 minutes at 5 to 10°C. The resulting mass was stirred at 5-10°C for the next 30 minutes. The separated solid was filtered and washed with diisopropyl ether (2 x 20 ml), and dried at 45-50°C to get stable polymorphic Form I of donepezil hydrochloride.

Yield: 9.3 gm

HPLC Purity: More than 99.9%.

## EXAMPLE 4

## PREPARATION OF STABLE POLYMORPHIC FORM I OF DONEPEZIL HYDROCHLORIDE

A mixture of crude donepezil hydrochloride (10 gm) in methanol (70 ml) was heated to 65°C to get a clear solution. The clear solution was cooled to 20°C and to it pre-cooled (5-10°C) diisopropyl ether (120 ml) was added over 15 minutes at 5 to 10°C. The resulting mass was stirred at 5-10°C for the next 30 minutes. The separated solid was filtered and washed with diisopropyl ether (2 x 20 ml), and dried at 45-50°C to get stable polymorphic Form I of donepezil hydrochloride.

Yield: 9.4 gm

HPLC Purity: More than 99.9%.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention. For example, the compounds described herein can be formulated into dosage forms that are suitable for administering to patients in need of the compound for treating a medical condition for which the compound is indicated, approved, or otherwise beneficial. Specifically, the stable Form I of donepezil hydrochloride can be formulated with one or more pharmaceutically acceptable excipients into a dosage form and administered to treat Alzheimer's type dementia.

We Claim:

1. A stable polymorphic Form I of donepezil hydrochloride.

2. The stable polymorphic Form I of donepezil hydrochloride of claim 1, wherein the donepezil hydrochloride has no detectable quantity of other polymorphic forms of donepezil hydrochloride.

3. The stable polymorphic Form I of donepezil hydrochloride of claim 1, wherein the donepezil hydrochloride has 2% or less of other polymorphic forms of donepezil hydrochloride.

4. The stable polymorphic Form I of donepezil hydrochloride, wherein the donepezil hydrochloride is incorporated into a dosage form with one or more pharmaceutically acceptable excipients.

5. A process for preparation of stable Form I of donepezil hydrochloride wherein the process comprises:

a) adding an optionally pre-cooled anti-solvent to a solution of donepezil hydrochloride at 30°C or less,

b) rapidly cooling the resultant solution; and

c) isolating Form I of donepezil hydrochloride from the reaction mass thereof.

6. The process of claim 5, wherein the anti-solvent is characterized by the donepezil hydrochloride being insoluble, practically insoluble or very slightly soluble in the anti-solvent.

7. The process of claim 6, wherein the anti-solvent comprises diisopropyl ether or diethyl ether.

8. The process of claim 5, wherein the solution of step b) is cooled to 25°C or less.

9. The process of claim 8, wherein the cooling is effected in 30 minutes or less.

10. The process of claim 5, wherein the donepezil hydrochloride has no detectable quantity of other polymorphic forms of donepezil hydrochloride.

11. The process of claim 5, wherein the donepezil hydrochloride has 2% or less of other polymorphic forms of donepezil hydrochloride.

12. A pharmaceutical composition comprising stable polymorphic Form I of donepezil hydrochloride and one or more pharmaceutically acceptable excipients and diluents, wherein the donepezil hydrochloride has no tendency to convert to any other polymorphic form.

13. The pharmaceutical composition of claim 12, wherein the donepezil hydrochloride has no detectable quantity of other polymorphic forms of donepezil hydrochloride.

14. The pharmaceutical composition of claim 12, wherein the donepezil hydrochloride has 2% or less of other polymorphic forms of donepezil hydrochloride.

15. A method of treating mild to moderate dementia of Alzheimer's type, the method comprising administering to a mammal in need thereof a therapeutically effective amount of stable polymorphic Form I of donepezil hydrochloride having no tendency to convert to any other polymorphic form.

16. The method of claim 15, wherein the therapeutically effective amount of donepezil hydrochloride is in the form of a pharmaceutical composition comprising one or more pharmaceutically acceptable excipients and diluents.

17. The method of claim 15, wherein the donepezil hydrochloride has no detectable quantity of other polymorphic forms of donepezil hydrochloride.

18. The method of claim 15, wherein the donepezil hydrochloride has 2% or less of other polymorphic forms of donepezil hydrochloride.

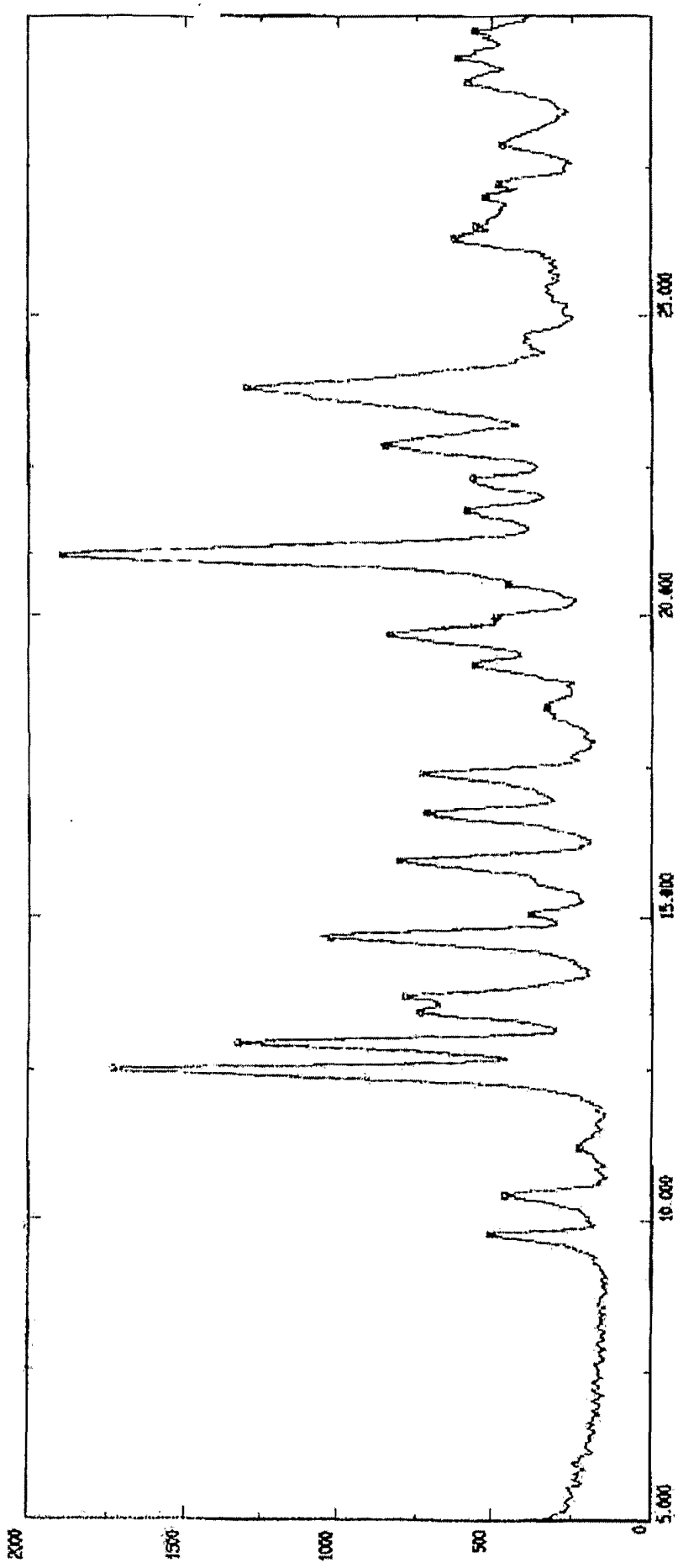



Figure 1

| Peak No. | 2Theta | FWHM | d-value | Intensity | I/Io | Peak No. | 2Theta | FWHN | d-value | Intensity | I/Io |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 9.760 | 0.212 | 9.0548 | 504 | 27 | 31 | 29.740 | ***** | 3.0015 | 552 | 29 |
| 2 | 10.400 | 0.212 | 8.4989 | 458 | 24 | | | | | | |
| 3 | 11.200 | ***** | 7.8936 | 231 | 12 | | | | | | |
| 4 | 12.500 | 0.188 | 7.0754 | 1732 | 92 | | | | | | |
| 5 | 12.940 | 0.212 | 6.8358 | 1323 | 70 | | | | | | |
| 6 | 13.440 | 0.188 | 6.5826 | 741 | 39 | | | | | | |
| 7 | 13.700 | 0.141 | 6.4583 | 788 | 42 | | | | | | |
| 8 | 14.660 | 0.094 | 6.0374 | 1027 | 54 | | | | | | |
| 9 | 14.700 | 0.212 | 6.0211 | 1027 | 54 | | | | | | |
| 10 | 15.040 | ***** | 5.8857 | 383 | 20 | | | | | | |
| 11 | 15.940 | 0.188 | 5.5554 | 807 | 43 | | | | | | |
| 12 | 16.740 | 0.259 | 5.2917 | 718 | 38 | | | | | | |
| 13 | 17.380 | 0.212 | 5.0982 | 733 | 39 | | | | | | |
| 14 | 18.480 | ***** | 4.7972 | 331 | 17 | | | | | | |
| 15 | 19.180 | 0.235 | 4.6236 | 555 | 29 | | | | | | |
| 16 | 19.680 | 0.306 | 4.5073 | 838 | 44 | | | | | | |
| 17 | 19.960 | 0.188 | 4.4447 | 486 | 26 | | | | | | |
| 18 | 20.520 | ***** | 4.3246 | 448 | 24 | | | | | | |
| 19 | 21.020 | 0.376 | 4.2229 | 1891 | 100 | | | | | | |
| 20 | 21.760 | 0.306 | 4.0809 | 579 | 31 | | | | | | |
| 21 | 22.300 | 0.188 | 3.9833 | 560 | 30 | | | | | | |
| 22 | 22.840 | 0.376 | 3.6903 | 852 | 45 | | | | | | |
| 23 | 23.800 | 0.212 | 3.7355 | 1296 | 69 | | | | | | |
| 24 | 26.280 | 0.235 | 3.3884 | 620 | 33 | | | | | | |
| 25 | 26.500 | ***** | 3.3607 | 551 | 29 | | | | | | |
| 26 | 27.000 | ***** | 3.2996 | 517 | 27 | | | | | | |
| 27 | 27.200 | ***** | 3.2758 | 476 | 25 | | | | | | |
| 28 | 27.840 | ***** | 3.2019 | 462 | 24 | | | | | | |
| 29 | 28.880 | ***** | 3.0890 | 574 | 30 | | | | | | |
| 30 | 29.280 | ***** | 3.0477 | 609 | 32 | | | | | | |

Figure 2

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/000416

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/32 A61K31/445 A61P25/28

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)
C07D 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, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EP 1 211 243 A (EISAI CO., LTD)<br>5 June 2002 (2002-06-05)<br>abstract<br>paragraph [0031]; examples 1-8,29-44<br>in particular examples 1-3,8,37-40,43<br>paragraph [0147] - paragraph [0152]<br>claims 1,9-12; figures 1,21 | 1-18 |
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| X | JP 10 053576 A (EISAI CO LTD; EISAI KAGAKU KK) 24 February 1998 (1998-02-24)<br>abstract | 1-18 |

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 19 July 2006 | 28/07/2006 |

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# INTERNATIONAL SEARCH REPORT

formation on patent family members

Inte[redacted]ional application No
PCT/IB2006/000416

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