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SECRETARÍA DE INDUSTRIA Y COMERCIO



07-076.543

SECRETARÍA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

BOGOTÁ, D.C. - COLOMBIA

Señor

**SUPERINTENDENTE DE INDUSTRIA Y
DIVISIÓN DE NUEVAS CREACIONES**

E. S. D.

Expediente No.: **07-076.543**
Patente de Invención: **"Cristales de (1RS, 3RS, 6RS)-
6- dimetilaminometil-1-(3-
metoxy-fenil)ciclohexano-1 ,3-
diol hidrocclorida"**
Titular: **GRÜNENTHAL GmbH**

DESTINO: 09

HUMBERTO RUBIO CAMACHO, mayor de edad, domiciliado en Bogotá, D.C., identificado con la cédula de ciudadanía número 17.192.062 de Bogotá, abogado en ejercicio, portador de la Tarjeta Profesional No. 50.007 expedida por el Consejo Superior de la Judicatura, actuando en carácter de **APODERADO** de la Sociedad **GRÜNENTHAL GmbH** domiciliada en Zieglerstrasse 6, 52078 Aachen, Alemania; encontrándome dentro de la debida oportunidad procesal y con el ánimo de complementar la solicitud de registro de la patente de invención mencionada en la referencia, la cual fue radicada ante su Despacho el 26 de Julio de 2007, me permito anexar:

- 1.- Copia de la Publicación Internacional No. WO 2006/089708 de 31 de Agosto de 2006 (Versión corregida)
- 2.- Copia del reporte Preliminar Internacional de Patentabilidad (Cap I - Form. PCT/IB/373)
- 3.- Copia de la Opinión Escrita de la autoridad encargada del reporte de búsqueda internacional.

Teniendo en cuenta lo anterior solicito se continúe con el trámite correspondiente.

Atentamente,

HUMBERTO RUBIO CAMACHO
C.C. 17.192.062 de Bogotá
T.P. 50.007 Consejo Superior
de la Judicatura.
COD. 4134

07/1249/P000667
BAP



CORRECTED VERSION

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(81) Designated States (unless otherwise indicated, for every
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CO, CR, CU, CZ, 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,
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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: CRYSTALLINE FORMS OF (1RS,3RS,6RS) 6-DIMETHYLAMINOMETHYL-1-(3-METHOXY-
CYCLOHEXANE-1,3-DIOL HYDROCHLORIDE

(57) Abstract: This invention relates to solid crystalline forms of (1 RS,3RS,6RS)-6- Dimethylaminomethyl-1-(3-methoxy-
phenyl)cyclohexane-1,3-diol hydrochloride (1), methods of producing 1, methods of use of 1, use of 1 as analgesics and
pharmaceutical compositions comprising 1.

WO 2006/089708 A1

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference GRA 3110-PCT	FOR FURTHER ACTION See item 4 below	
International application No. PCT/EP2006/001548	International filing date (<i>day/month/year</i>) 21 February 2006 (21.02.2006)	Priority date (<i>day/month/year</i>) 25 February 2005 (25.02.2005)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant GRÜNENTHAL GMBH		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☒ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☒ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Date of issuance of this report 28 August 2007 (28.08.2007)
	Authorized officer Agnes Wittmann-Regis e-mail: pt06.pct@wipo.int

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To: -

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2006/001548

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25.02.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07C217/54 A61K31/135

Applicant
GRÜNENTHAL GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No. ⁵⁸
PCT/EP2006/001548

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2006/001548

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ not paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-56
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-56
Industrial applicability (IA)	Yes: Claims	1-56
	No: Claims	

2. Citations and explanations

see separate sheet

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2006/001548

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV

Lack of unity of invention

- D1: EP-A-0 753 506 (GRUENENTHAL GMBH) 15 January 1997 (1997-01-15)
D2: US-A-5 733 936 (BUSCHMANN ET AL) 31 March 1998 (1998-03-31)
D3: US R E37 355 E1 (BUSCHMANN HELMUT HEINRICH ET AL) 4 September
2001 (2001-09-04)
D4: WO 2005/009329 A (GRUENENTHAL GMBH; BARTHOLOMAEUS,
JOHANNES) 3 February 2005 (2005-02-03)

Claimed are different crystalline form of (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)cyclohexane-1,3-diol hydrochloride.

The technical feature common to all claimed crystalline forms is the chemical structure of (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)cyclohexane-1,3-diol hydrochloride.

(1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)cyclohexane-1,3-diol hydrochloride however is already known from D1-D4.

The different crystalline forms of (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)cyclohexane-1,3-diol hydrochloride then are not linked by a common technical feature.

Hence the Search Examiner considers that the following separate inventions or groups of inventions are not so linked as to form a single general inventive concept:

1. Crystalline form A of (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)cyclohexane-1,3-diol hydrochloride as well as its synthesis, compositions comprising this compound and its use (claims 1-7 and 34-36 in part).
2. Crystalline form B of (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)cyclohexane-1,3-diol hydrochloride as well as its synthesis, compositions comprising this compound and its use (claims 8-14 and 34-36 in part).

3. Crystalline form C of (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)cyclohexane-1,3-diol hydrochloride as well as its synthesis, compositions comprising this compound and its use (claims 15-21 and 34-36 in part).
4. Crystalline form D of (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)cyclohexane-1,3-diol hydrochloride as well as its synthesis, compositions comprising this compound and its use (claims 22-27 and 34-36 in part).
5. Crystalline form E of (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)cyclohexane-1,3-diol hydrochloride as well as its synthesis, compositions comprising this compound and its use (claims 28-33 and 34-36 in part).

The applicant is asked to state upon which invention or group of inventions further prosecution of the application should be based and to limit the application accordingly. The other inventions are to be excised from the claims, description and drawings if any.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Novelty (Article 33(2) PCT):

Claimed are different specific crystalline forms of (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)cyclohexane-1,3-diol hydrochloride, methods for synthesizing said compounds, compositions and medicaments comprising said compounds, as well as their use for the production of a medicament.

These specific crystalline structures are not known from D1-D4.

The subject-matter of claims 1-56 therefore is considered novel.

2. Inventive Step (Article 33(3) PCT):

(1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)cyclohexane-1,3-diol

hydrochloride and its use in the treatment of pain, urinary incontinence, depression and anxiety are well known from the prior art.

The difference between the compound known from the prior art (D1-D4) then is the different crystalline form of the compounds claimed.

The description does not describe a new or improved activity of the claimed compounds in comparison with the known form of (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)cyclohexane-1,3-diol hydrochloride.

The technical problem then can be seen in providing alternative compounds having similar biological activity.

It is part of the general knowledge of the person skilled in the art that polymorphs commonly have the same/similar biological activity. Routine screening of possible polymorphs usually is carried out to find new alternative crystalline forms.

The solution of the technical problem claimed in claims 1-56 therefore is considered obvious.

The subject-matter of claims 1-56 then cannot be considered inventive.

Re Item VII

Certain defects in the international application

Claims 3, 5, 12, 14, 22, 24, 34, 35, 42 and 43 contain references to the drawings. According to Rule 6.2 (a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

Re Item VIII

Certain observations on the international application

1. Since a specific polymorph is considered fully characterized by a powder diffraction pattern, the claims relating to additional Raman spectrum information is redundant.

The subject-matter of claims 4, 5, 13, 14, 23, 24, 35 and 31 do not fulfil the

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2006/001548

requirements of Article 6 PCT.

2. In claims 26 and 27 the upper temperature limit is disclosed as "xx" instead of as a specific numeric value. The subject-matter of these claims therefore lacks clarity.
3. The subject-matter of claims 9, 19, 31, 39 and 49 relates to specific crystalline forms of (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)cyclohexane-1,3-diol hydrochloride obtainable by a particular process.

The different specific crystalline forms of (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)cyclohexane-1,3-diol hydrochloride are already claimed in claims 1, 10, 20, 32 and 40. The subject-matter of claims 9, 19, 31, 39 and 49 then is
redundant.