



Industria y Comercio
SUPERINTENDENCIA

PCT

SOLICITUD

PATENTE DE INVENCION

03-69583

21 EXPEDIENTE N°

54 TÍTULO SALES DE ADICION DE ACIDO MALICO DE TERBINAFTNA

51 CLASIFICACIÓN INTERNACIONAL

C 07

A61K31/135

71 SOLICITANTE

NOVARTIS AG

DOMICILIO

BASILEA, SUIZA

74 APODERADO

JIMENA ESCOBAR URIBE

22 BOGOTÁ D C.

AGOSTO 13 2009

5

Industria y Comercio
SUPERINTENDENCIA



03 069583 00

SUPERINDUSTRIA Y COMERCIO
Radicación: 03069583 00000000 Folios: 99
Fecha (AMD): 2003-08-13 16:06:23
Trámite: 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:



Patente de invención



Patente de Modelo de Utilidad



Capítulo I



Capítulo II

2

S LICITANTE
(71)

Nombre: **NOVARTIS AG**

Dirección: Lichtstrasse 35

Nacionalidad o Domicilio: CH -4056 Basilea,
Suiza.

Lugar de Constitución: Suiza

Teléfono: 4161324111 Fax: 41613227532

E-mail

IDENTIFICACIÓN

C.C. ☐

NIT ☐

C.E. ☐

Otro ☐

Número

3

REPRESENTANTE
AP DERADO
(74)

Nombre: JIMENA ESCOBAR URIBE

Dirección: Cra. 11A No. 94-76 (Of. 305)

Teléfono: 6 162051/61 Fax: 6 161889

E-mail: tm-patent@escobaruribe.com

IDENTIFICACIÓN

C.C. ☒

NIT ☐

C.E. ☐

Otro ☐

Número 39.779.452T.P 68228

4

INVENTOR (ES)
(72)

Nombre: **VER ANEXOS**

Dirección:

Nacionalidad o domicilio:

5

PCT (86)

Solicitud Internacional No. PCT/EP02/01249

Fecha Febrero 6, 2002

Publicación Internacional No WO 02/070455 A1

Fecha Septiembre 12, 2002

6 **TÍTULO (54)** SALES DE ADICIÓN DE ÁCIDO MÁLICO DE TERBINAFINA.

7 **Clasificación Internacional (51)**

C 07C 211/30 ; A61K31/135

8 **Prioridad**

SI ☒ NO ☐

(33) País de Origen

GRAN BRETAÑA

(Reino Unido)

(32) Fecha

Febrero 7, 2001

(31) Número de Solicitud

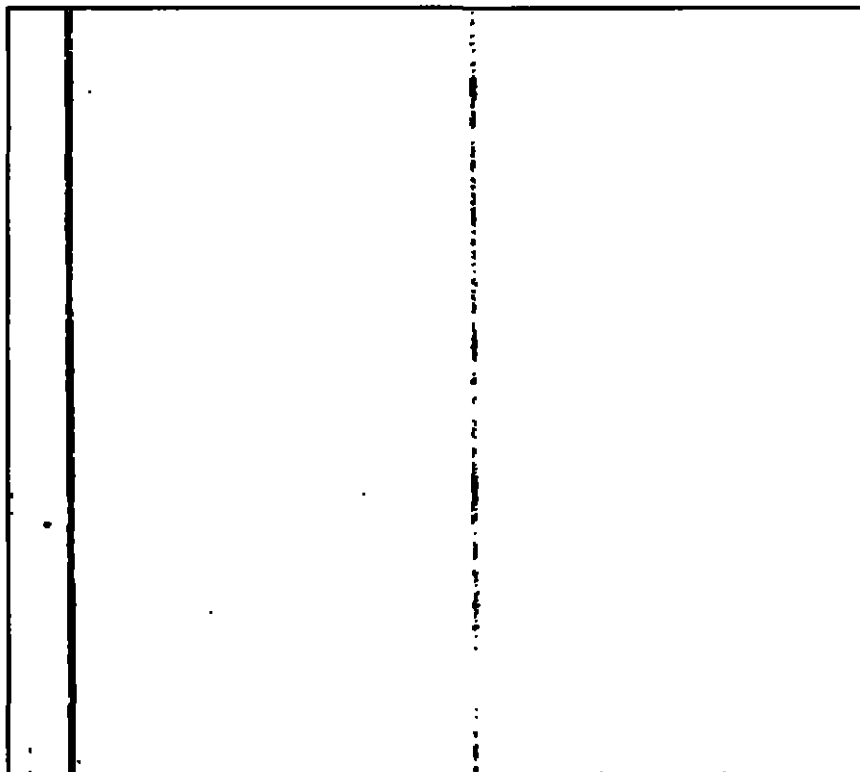
0103046.9

9 **Comprobante de pago N.** 03 - 52.295

Fecha Julio 25, 2003

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☒ Documento que acredite la existencia y representación legal cuando el solicitante sea persona Prot. 17.398
- ☒ Poderes si fuere el caso Protocolo No. 17.398
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- ☒ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso copia de contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 X 12 .
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional
- ☐ Otros

11 FIGURA CARACTERÍSTICA



12 Solicito la concesión de la patente

NOMBRE: JIMENA ESCOBAR URIBE

FIRMA: 

C.C. 39.779.452 DE Usaquén T.P. 68.228

As. 2584/PCT

2584

2

SUPERINDUSTRIA Y COMERCIO
Radicación : 83069583 00000000 Folios: 99
Fecha (AMD): 2003-08-13 16:06:23
Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

NIT : 000174089-2

RECIBO OFICIAL DE CAJA : 03 - 32,293
FECHA : JULIO 23 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ESCOBAR URIBE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	4041888	24/07/2003	5,104,000.00

***** CONCEPTO *****

CANT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
	TOTAL :	400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ANEXOS

INVENTORES

**1.) DANIELLE GIRON
(68100 Mulhouse, Francia);**

**2.) JEAN-LOUIS REBER
(68680 Kembs, Francia);**

**3.) STEFAN HIRSCH
(79539 Lörrach, Alemania).**

4

Solicito expresamente a nombre de la sociedad
NOVARTIS AG., sociedad constituida de
conformidad con las leyes de Suiza, domiciliada en
Lichtstrasse 35, CH-4056 Basilea, Suiza, el
otorgamiento de Patente para la invención titulada
**"SALES DE ADICIÓN DE ÁCIDO MÁLICO DE
TERBINAFINA"**.

Clase: C 07


JIMENA ESCOBAR URIBE
C.C. 39.779.452 de Usaquen
T.P. 68.228

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

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
12 September 2002 (12.09.2002) ✓

PCT

(10) International Publication Number
WO 02/070455 A1 ✓(51) International Patent Classification⁷: C07C 211/30,
A61K 31/13514, F-68680 Kaysersberg (FR). HIRSCH, Stefan (DE/DE);
Theodor-Heuss-Strasse 21A, 79539 Lörrach (DE).

(21) International Application Number: PCT/EP02/01249 ✓

(74) Agent: BECKER, Konrad; Novartis AG, Corporate In-
tellectual Property, Patent & Trademark Dept., CH-4002
Basel (CH).

(22) International Filing Date: 6 February 2002 (06.02.2002) ✓

(25) Filing Language: English

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, ~~CO~~, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH,
PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA,
US, UZ, VN, YU, ZA, ZW.

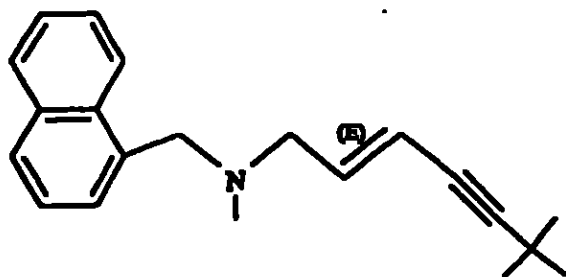
(26) Publication Language: English

(30) Priority Data: ✓
0103046.9 ✓ 7 February 2001 (07.02.2001) GB ✓(71) Applicant (*for all designated States except AT, US*): NO-
VARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel
(CH). ✓(84) Designated States (*regional*): Russian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,
CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,
NL, PT, SI, TR).(71) Applicant (*for AT only*): NOVARTIS-ERFINDUNGEN
VERWALTUNGSGESELLSCHAFT M.B.H. [AT/AT];
Brunner Strasse 59, A-1230 Vienna (AT).Published:
.. with international search report

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): GIRON, Danielle
[FR/FR]; Rue du Silikon 9, F-68100 Mulhouse (FR).
REBER, Jean-Louis [FR/FR]; Rue de la PromenadeFor two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: MALIC ACID ADDITION SALTS OF TIRBINAFINI



(1)

(57) Abstract: The invention concerns
salts of the compound of formula (I) with
malic acid, their preparation, corresponding
pharmaceutical compositions and their use as
antimycotics.

WO 02/070455 A1

(12) SOLICITUD INTERNACIONAL PUBLICADA DE ACUERDO CON EL TRATADO DE COOPERACIÓN
EN MATERIA DE PATENTES (TCP)
OMPI

(19) Organización Mundial de la Propiedad Intelectual Oficina Internacional	TCP	(10) Número de la Publicación Internacional: WO 02/070455 A1
(43) Fecha de la Publicación Internacional: 12 de septiembre de 2002 (12.09.2002)		
(51) Clasificación de Patente Internacional ¹ : C07C 211/30, A61K 31/135		(74) Agente: BECKER, Konrad; Novartis AG, Corporación de Propiedad Intelectual, Departamento de Patentes y Marcas, CH-4002 Basel (CH).
(21) Número de Solicitud Internacional: PCT/EP02/01249		(81) Estados Designados (nacionales): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VN, YU, ZA, ZW.
(22) Fecha de Presentación Internacional: 6 de febrero de 2002 (06.02.2002)		(84) Estados Designados (regionales): Patente Eursalónica (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).
(25) Idioma de Presentación: Inglés		Publicado: - con reporte de búsqueda internacional
(26) Idioma de Publicación: Inglés		Para los códigos de dos letras y otras abreviaturas, refiérase a las "Notas de Guía sobre Códigos y Abreviaturas" que aparecen al principio de cada publicación regular de la Gaceta TCP.
(30) Información de Prioridad: 0103046.9 07 de febrero de 2001(07.02.2001) GB		
(71) Solicitante: (para todos los Estados designados excepto AT, US): NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).		
(71) Solicitante: (solo para AT): NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H. [AT/AT]: Brunner Strasse 59, A-1230 Vienna (AT).		
(72:) Inventores; y		
(75) Inventores/Solicitantes (solo para US): GIRON, Danielle [FR/FR]: Rue du Sillon 9, F-68100 Mulhouse (FR). REBER, Jean-Louis [FR/FR]: Rue de la Promenade 14, F-68680 Kembs (FR). HIRSCH, Stefan [DE/DE]: Theodor-Heuss-Strasse 21*, 79539 Lörrach (DE).		
 (1) (54) Título: SALES DE ADICIÓN DE ÁCIDO MÁLICO DE TERBINAFINA (57) Resumen: La invención se refiere a sales del compuesto de la fórmula I con ácido málico, a su preparación, a composiciones farmacéuticas correspondientes, y a su uso como antimicóticos.		

WO 02/070455 A1

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT**CHAPTER II****DEMAND**

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 4-31862A	
International application No. PCT/EP 02/01249	International filing date (day/month/year) 8 February 2002 (08.02.02)	(Earliest) Priority date (day/month/year) 7 February 2001 (07.02.01)	
Title of invention MALIC ACID ADDITION SALTS OF			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.) Novartis AG Lichtstrasse 35 4058 Basel CH		Telephone No. +4161 324 11 11	
		Facsimile No. +4161 322 75 32	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality: CH		State (that is, country) of residence: CH	
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.) Novartis-Erfindungen Verwaltungsgesellschaft m.b.H. Brunner Strasse 59 1230 Vienna AT			
State (that is, country) of nationality: AT		State (that is, country) of residence: AT	
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.) GIRON, Danielle Rue du Sillon 9 68100 Mulhouse FR			
State (that is, country) of nationality: FR		State (that is, country) of residence: FR	
☒ Further applicants are indicated on a continuation sheet.			

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

REBER, Jean-Louis
Rue de la Promenade 14
68680 Kembs
FR

State (that is, country) of nationality:
FR

State (that is, country) of residence:
FR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HIRSCH, Stefan
Theodor-Heuss-Strasse 21A
79539 Lörrach
DE

State (that is, country) of nationality:
DE

State (that is, country) of residence:
DE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
and ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☒ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)

GROS, Florent
Novartis AG
Corporate Intellectual Property
Patent & Trademark Department
4002 Basel
CH

Telephone No.

+4161 324 11 11

Facsimile No.

+4161 322 75 32

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments: *

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☐ as originally filed
☐ as amended under Article 34

the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☒ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Sheet No. 4.

International application No.
PCT/EP 02/01249

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary
Examining Authority use only

- | received | not received |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☒ other (specify): copy of general sub-authorisation |
| 4. ☐ copy of general power of attorney; reference number, if any: | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

In the name of the applicants
The representative


30.07.2002

GROS, Florent AV 36671 + 37586

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due
to CORRECTIONS under Rule 60.1(b):3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months
from the priority date and item 4 or 5, below, does not apply.☐ The applicant has been
informed accordingly.4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of
Rule 80.5.5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival
is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

CHAPTER II

PCT

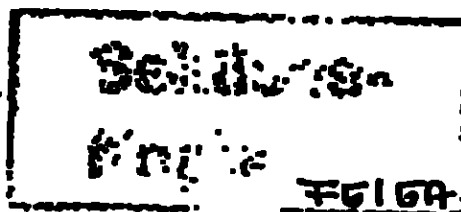
FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/EP 02/01249	For International Preliminary Examining Authority use only
Applicant's or agent's file reference 4-31862A	Date stamp of the IPEA
Applicant Novartis AG et al.	
CALCULATION OF PRESCRIBED FEES	
1. Preliminary examination fee	EUR 1530.- P
2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>)	EUR 159.- H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EUR 1689.- TOTAL
MODE OF PAYMENT	
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash
☐ cheque	☐ revenue stamps
☐ postal money order	☐ coupons
☐ bank draft	☐ other (specify):
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT <i>(This mode of payment may not be available at all IPEAs)</i>	
☒ Authorization to charge the total fees indicated above.	IPEA/ EP _____
☒ <i>(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)</i> Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	Deposit Account No.: 2811 0031
	Date: 30.07.2002
	Name: Novartis AG
	Signature: <u><i>Hans Altmann</i></u>



European Patent Office
D-80298 Munich



14 March 2000

Your Ref:

Our Ref:
HOGM

General sub-authorisations

Dear Sirs,

I, Konrad Becker, authorised under the following General Authorisations:

Novartis AG	38871
Systemix Inc.	39505
Genetic Therapy Inc.	39407
Imutran Ltd.	39104
Biochemie GmbH	37946
The Scripps Research Institute	37685
Novartis Erfindungen Verwaltungsgee. mbH	37686
Ciba-Geigy Japan Ltd.	37441
Novartis Consumer Health	37125

do hereby sub-authorise

Florent Gros (EPO code no. 87080)
c/o Novartis AG
Corporate Intellectual Property
Patent and Trademark Department
CH-4002 Basel
Switzerland

to represent the authorisers in all proceedings established by the EPC and to act for the authorisers in all patent transactions and to receive payments on their behalf. These sub-authorisations shall also apply to the same extent to any proceedings established by the Patent Cooperation Treaty.

Yours faithfully
NOVARTIS AG

Dr. Konrad Becker
Head of Patent & Trademark Department

4-31862/PCT D

PATENT COOPERATION TREATY

P + TM Dept.

- 2 April 2002

PCT

From the RECEIVING OFFICE

To:

Becker, Konrad
NOVARTIS AG
Corporate Intellectual Property
Patent & Trademark Department
CH-4002 Basel
SUISSE

APR 2 2002
M/D F/L PS/TS
Replen:

NOTIFICATION OF THE INTERNATIONAL
APPLICATION NUMBER AND OF THE
INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

Date of mailing
(day/month/year)

28. 03. 2002

Applicant's or agent's file reference

4-31862A

IMPORTANT NOTIFICATION

International application No.

PCT/EP 02/01249

International filing date (day/month/year)

06/02/2002

Priority date (day/month/year)

07/02/2001

Applicant

NOVARTIS AG

Title of the invention

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.
2. The applicant is further notified that the record copy of the international application was transmitted to the International Bureau on the above date of mailing.

3. ☐ Other: _____

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(e)).

Name and mailing address of the Receiving Office



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized official

[Signature]

* M. Kr.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/EP 0 2 / 0 1 2 4 9..

International Application No.

06 FEB 2002

International Filing Date

06 02 2002

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 4-31862A

Box No. I TITLE OF INVENTION ORGANIC COMPOUNDS	
Box No. II APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.)	
Novartis AG Lichtstrasse 35 4056 Basel CH	Telephone No. +41 61 324 11 11 Facsimile No. +41 61 322 75 32 Teleprinter No. Applicant's registration No. with the Office
State (that is, country) of nationality: CH	State (that is, country) of residence: CH
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.)	
Novartis-Erfindungen Verwaltungsgesellschaft m.b.H. Brunner Strasse 59 1230 Vienna AT	This person is: ☒ applicant only ☐ applicant and inventor ☐ inventor only (if this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: AT	State (that is, country) of residence: AT
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box	
☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
BECKER, Konrad Novartis AG Corporate Intellectual Property Patent & Trademark Department 4002 Basel CH	Telephone No. +41 61 324 11 11 Facsimile No. +41 61 322 75 32 Teleprinter No. Agent's registration No. with the Office
☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

Sheet No. ...2...

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.) GIRON, Danielle Rue du Sillon 9 68100 Mulhouse FR	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: FR	State (that is, country) of residence: FR
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.) REBER, Jean-Louis Rue de la Promenade 14 68680 Kembs FR	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: FR	State (that is, country) of residence: FR
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.) HIRSCH, Stefan Theodor-Heuss-Strasse 21A 79539 Lörrach DE	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.)	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☐ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|---|--|---|
| ☒ AE United Arab Emirates | ☐ GM Gambia | ☒ NZ New Zealand |
| ☒ AG Antigua and Barbuda | ☒ HR Croatia | ☐ OM Oman |
| ☒ AL Albania | ☒ HU Hungary | ☒ PH Philippines |
| ☒ AM Armenia | ☒ ID Indonesia | ☒ PL Poland |
| ☒ AT Austria | ☒ IL Israel | ☒ PT Portugal |
| ☒ AU Australia | ☒ IN India | ☒ RO Romania |
| ☒ AZ Azerbaijan | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BA Bosnia and Herzegovina | ☒ JP Japan | ☐ SD Sudan |
| ☒ BB Barbados | ☒ KE Kenya | ☒ SE Sweden |
| ☒ BG Bulgaria | ☒ KG Kyrgyzstan | ☒ SG Singapore |
| ☒ BR Brazil | ☒ KP Democratic People's Republic of Korea | ☒ SI Slovenia |
| ☒ BY Belarus | ☒ KR Republic of Korea | ☒ SK Slovakia |
| ☒ BZ Belize | ☒ KZ Kazakhstan | ☐ SL Sierra Leone |
| ☒ CA Canada | ☒ LC Saint Lucia | ☒ TJ Tajikistan |
| ☒ CH & LI Switzerland and Liechtenstein | ☒ LK Sri Lanka | ☒ TM Turkmenistan |
| ☒ CN China | ☐ LR Liberia | ☒ TN Tunisia |
| ☒ CO Colombia | ☐ LS Lesotho | ☒ TR Turkey |
| ☒ CR Costa Rica | ☒ LT Lithuania | ☒ TT Trinidad and Tobago |
| ☒ CU Cuba | ☒ LU Luxembourg | ☐ TZ United Republic of Tanzania |
| ☒ CZ Czech Republic | ☒ LV Latvia | ☒ UA Ukraine |
| ☒ DE Germany | ☒ MA Morocco | ☐ UG Uganda |
| ☒ DK Denmark | ☒ MD Republic of Moldova | ☒ US United States of America |
| ☒ DM Dominica | ☐ MG Madagascar | ☐ UZ Uzbekistan |
| ☒ DZ Algeria | ☒ MK The former Yugoslav Republic of Macedonia | ☒ VN Viet Nam |
| ☒ EC Ecuador | ☒ MN Mongolia | ☒ YU Yugoslavia |
| ☒ EE Estonia | ☐ MW Malawi | ☒ ZA South Africa |
| ☒ ES Spain | ☒ MX Mexico | ☐ ZM Zambia |
| ☒ FI Finland | ☒ MZ Mozambique | ☒ ZW Zimbabwe |
| ☒ GB United Kingdom | ☒ NO Norway | |
| ☒ GD Grenada | | |
| ☒ GE Georgia | | |
| ☒ GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- | | | |
|--------------------------------|--------------------------------|--------------------------------|
| ☐ | ☐ | ☐ |
| ☐ | ☐ | ☐ |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Supplemental Box

If the Supplemental Box is not used, this sheet should not be included in the request.

1. If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

Continuation of Box No. II

Novartis AG is applicant for all designated States with the exception of: AT (Austria) and US (USA)

- (IV) more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

Continuation of Box No. III

Novartis-Erfindungen Verwaltungsgesellschaft m.b.H. is applicant for AT (Austria) only.

- (II) If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
- (III) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor-applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
- (IV) If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
- (V) If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
- (VI) If, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.
2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
Item (1) 07 February 2001 (07.02.01)	0103046.9	GB		
Item (2)				
Item (3)				
Item (4)				
Item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☐ Item (1) ☐ Item (2) ☐ Item (3) ☐ Item (4) ☐ Item (5) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(11)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA /

Request to use results of earlier search; reference to that search (If an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

Number of
declarations

- | | | |
|---|--|---|
| ☐ Box No. VIII (i) | Declaration as to the identity of the inventor | : |
| ☐ Box No. VIII (ii) | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | : |
| ☐ Box No. VIII (iii) | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | : |
| ☐ Box No. VIII (iv) | Declaration of inventorship (only for the purposes of the designation of the United States of America) | : |
| ☐ Box No. VIII (v) | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | : |

Sheet No. ...9...

Box No. IX CHECK LIST; LANGUAGE OF FILING		
This international application contains: (a) the following number of sheets in paper form: request (including declaration sheets) : 6 description (excluding sequence listing part) : 14 claims : 1 abstract : 1 drawings : 6 Sub-total number of sheets : 28 sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below) : 0 Total number of sheets : 28 (b) sequence listing part of description filed in computer readable form (i) ☐ only (under Section 801(a)(i)) (ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii)) Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(ii), in right column):		This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item): 1. ☒ fee calculation sheet : 1 2. ☐ original separate power of attorney : 3. ☐ original general power of attorney : 4. ☒ copy of general power of attorney; reference number, if any: AV.36671 + 37586 : 2 5. ☐ statement explaining lack of signature : 6. ☒ priority document(s) identified in Box No. VI as item(s): : 1 7. ☐ translation of international application into (language): : 8. ☐ separate indications concerning deposited microorganism or other biological material : 9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other)) : (i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) : (ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter : (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column : 10. ☐ other (specify): :
Figure of the drawings which should accompany the abstract:	Language of filing of the international application: <u>english</u>	
Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE <i>Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).</i>		
In the name of the applicants The representative <u>H. Becker</u> BECKER, Konrad, AV 36671 + 37586		
04.02.2002		

For receiving Office use only	
1. Date of actual receipt of the purported international application: <u>06 FEB 2002</u> (<u>06.02.02</u>)	2. Drawings: ☒ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 1(2):	
5. International Searching Authority (if two or more are competent): <u>ISA /</u>	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

21.07.2002
4-31862A
Lucien Vallet

VT
PCT
EP02/01249

P + TM Dept.

21. Mai 2002

APPL M/D F/L PS/TS

Kopien:

From the INTERNATIONAL SEARCHING AUTHORITY

To:
NOVARTIS AG
Corporate Intellectual Property
Attn. Becker, Konrad
Patent & Trademark Department
CH-4002 Basel
SWITZERLAND

P +

TM Dept.

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

21. Mai 2002

(PCT Rule 44.1)

APPL M/D F/L PS/TS

Kopien:

Date of mailing
(day/month/year)

21/05/2002

Applicant's or agent's file reference

4-31862A

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/EP 02/01249

International filing date
(day/month/year)

06/02/2002

Applicant

NOVARTIS AG

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.36

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 30 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patenlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Peggy Frenzel

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the letter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 48.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 48.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 18, 19 and 20; new claims 21 and 22 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 18, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 18 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY
PCT

INTERNATIONAL SEARCH REPORT
(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 4-31862A	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 02/01249	International filing date (day/month/year) 06/02/2002	(Earliest) Priority Date (day/month/year) 07/02/2001
Applicant NOVARTIS AG		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:
MALIC ACID ADDITION SALTS OF TERBINAFINE

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant. ☐ None of the figures.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/01249

24

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07C211/30 A61K31/135		
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 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, BEILSTEIN Data, 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.
A	WO 98 43673 A (JOHNSON & JOHNSON CONSUMER) 8 October 1998 (1998-10-08) page 9 -page 10; claims 7,19; table 8	1
A	EP 0 318 860 A (BANYU PHARMA CO LTD) 7 June 1989 (1989-06-07) page 10, line 36 - line 40	1
A	EP 0 515 310 A (SANDOZ AG) 25 November 1992 (1992-11-25) cited in the application page 5 -page 9	1
A	EP 0 024 587 A (SANDOZ AG) 11 March 1981 (1981-03-11) page 16, line 22 - line 27; claims 1,11 -/-	1
☒ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "Z" document member of the same patent family		
Date of the actual completion of the international search 10 May 2002		Date of mailing of the international search report 21/05/2002
Name and mailing address of the ISA European Patent Office, P.O. 5818 Patentplan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl Fax: (+31-70) 340-3016		Authorized officer Rufet, J

26

PCT/EP 02/01249

Category •

Relevant to claim No.

WO 01 28976 A (BOD PETER ;DEMETER MARIA
(HU); VARGA KATALIN (HU); DOMANY GYORGY)
26 Apr 11 2001 (2001-04-26)
example 3

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/01249

27

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9843673	A	08-10-1998	
		AU 6677698 A	22-10-1998
		BR 9811458 A	19-09-2000
		CN 1252003 T	03-05-2000
		EP 0971746 A1	19-01-2000
		HU 0001739 A2	28-12-2000
		JP 2001518879 T	16-10-2001
		PL 335934 A1	22-05-2000
		WO 9843673 A1	08-10-1998
		ZA 9802662 A	30-09-1999
EP 0318860	A	07-06-1989	
		AT 90666 T	15-07-1993
		AU 2594488 A	29-06-1989
		CA 1319689 A1	29-06-1993
		DE 3881842 D1	22-07-1993
		DE 3881842 T2	04-11-1993
		DK 657988 A	28-05-1989
		EP 0318860 A2	07-06-1989
		IL 88473 A	21-02-1993
		NZ 227042 A	28-05-1991
		PT 89089 A ,B	01-12-1988
		US 5234946 A	10-08-1993
		CN 1037141 A	15-11-1989
		JP 3193746 A	23-08-1991
		ZA 8808792 A	30-08-1989
EP 0515310	A	25-11-1992	
		AT 400517 B	25-01-1996
		AT 102392 A	15-06-1995
		AU 647922 B2	31-03-1994
		AU 1631792 A	26-11-1992
		BR 1100213 A3	06-06-2000
		CA 2068957 A1	21-11-1992
		CH 683823 A5	31-05-1994
		CS 9201491 A3	16-12-1992
		CY 1942 A	16-05-1997
		CZ 285275 B6	16-06-1999
		DE 4215450 A1	26-11-1992
		EP 0515310 A1	25-11-1992
		FI 922252 A	21-11-1992
		FI 981777 A	18-08-1998
		FR 2676646 A1	27-11-1992
		GB 2255908 A ,B	25-11-1992
		HK 148896 A	16-08-1996
		HU 62466 A2	28-05-1993
		IE 921599 A1	02-12-1992
		IL 101903 A	16-08-1998
		IT 1260710 B	22-04-1996
		JP 2651311 B2	10-09-1997
		JP 5132419 A	28-05-1993
		LU 88114 A1	06-12-1993
		MX 9202328 A1	29-04-1994
		NO 180772 B	10-03-1997
		RO 111986 B1	30-04-1997
		SK 281615 B6	10-05-2001
		US 6005001 A	21-12-1999
		US 5681849 A	28-10-1997
		US 6121314 A	19-09-2000
		US 5856355 A	05-01-1999
		ZA 9203671 A	22-11-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/01249

28

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0515310	A	SK 281616 B6 RU 2093152 C1	10-05-2001 20-10-1997
EP 0024587	A	11-03-1981	
		AT 10272 T	15-11-1984
		AU 538928 B2	06-09-1984
		AU 6159280 A	16-04-1981
		CA 1157023 A1	15-11-1983
		CY 1410 A	22-04-1988
		DE 3069633 D1	20-12-1984
		DK 357980 A ,B,	23-02-1981
		EP 0024587 A1	11-03-1981
		ES 494408 D0	16-06-1981
		ES 8105694 A1	01-09-1981
		FI 802583 A ,B,	23-02-1981
		HK 21588 A	31-03-1988
		IE 50878 B1	06-08-1986
		IL 60877 A	31-08-1984
		JP 1730075 C	29-01-1993
		JP 4015216 B	17-03-1992
		JP 63313753 A	21-12-1988
		JP 1494302 C	20-04-1989
		JP 56032440 A	01-04-1981
		JP 63042612 B	24-08-1988
		KE 3775 A	27-11-1987
		LU 88343 A9	04-05-1994
		MY 18186 A	31-12-1986
		NZ 194714 A	09-11-1984
		PH 22166 A	28-06-1988
		PT 71717 A ,B	01-09-1980
		SG 89287 G	30-09-1988
		US 5132459 A	21-07-1992
		US 4755534 A	05-07-1988
		YU 209680 A1	31-10-1983
		ZA 8005185 A	31-03-1982
WO 0128976	A	26-04-2001	
		WO 0128976 A1	26-04-2001
		AU 6360499 A	30-04-2001

PATENT COOPERATION TREATY

ALL
PCT ✓

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
GROS, Florent
NOVARTIS AG
Corporate Intellectual Property
Patent & Trademark Department
CH-4002 Basel
SUISSE

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
P + TM Dept.
29 Aug. 2002

(PCT Rule 7.2)
APPL. M/D F/L PS/TS
Köplen:

Date of mailing
(day/month/year) 27/08/2002

Applicant's or agent's file reference
4-31862A

IMPORTANT NOTIFICATION

International application No.
PCT/EP 02/ 01249

International filing date (day/month/year)
06/02/2002

Priority date (day/month/year)
07/02/2001

Applicant

NOVARTIS AG et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27 (5), 33 (5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

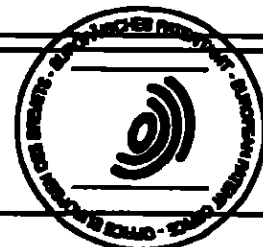
Name and mailing address of the IPEA/



European Patent Office, Gitschiner Str. 103
D-10969 Berlin - Germany
Tel: (+49-30) 25901-0
Fax: (+49-30) 25901-840

Authorized officer

KOSTER A H
Tel. (+49-89) 2399 2828



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 34 and Rule 70)

Applicant's or agent's file reference 4-31862A	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 02/ 01249	International filing date (day/month/year) 06/02/2002	Priority date (day/month/year) 07/02/2001
International Patent Classification (IPC) or national classification and IPC G07C211/30		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

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

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

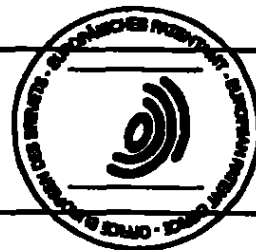
These annexes consists of a total of _____ sheets.

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

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 31/07/2002	Date of completion of this report 22/08/2002
Name and mailing address of the IPEA/  European Patent Office, Gluckstr. 103 D-10969 Berlin - Germany Tel.: (+49-30) 25901-0 Fax: (+49-30) 25901-840	Authorized officer DE BUNDEL E R J Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) (July 1998)



I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(a) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in the independent claims, which have been the subject of an international search report, meets the criteria mentioned in Article 33(1) PCT, i.e. appears to be novel, to involve an inventive step and to be industrially applicable.

TRATADO DE COOPERACION EN MATERIA DE PATENTES

PCT

INFORME EXAMEN PRELIMINAR INTERNACIONAL

(PCT artículo 36 y regla 70)

Referencia del solicitante o agente 4-31862A	Ver notificación de la transmisión del examen preliminar internacional (formato PCT/IPEA/416) PARA PROSEGUIR	
No. Solicitud Internacional PCT/ EP 02/ 01249	Fecha de presentación internacional (día/mes/año) 06/02/2002	Fecha de prioridad (día/mes/año) 07/02/2001
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC C07C211/30		
Solicitante NOVARTIS AG et al.		

1. Este examen preliminar internacional ha sido preparado por esta Autoridad encargada del Examen Preliminar Internacional y es transmitida al solicitante de acuerdo con el artículo 36.

2. Este INFORME consiste de un total de 2 páginas, incluyendo esta hoja.

___ Este informe también está acompañado por ANEXOS, esto es hojas de la descripción, reivindicaciones y/o dibujos, los cuales han sido modificados y son la base para este informe y/o hojas que contienen rectificaciones presentadas ante esta Autoridad (ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas bajo el PCT).

Estos anexos consisten en un total de ___ hojas.

3. Este informe contiene indicaciones que se relacionan con los siguientes puntos:

- I. ☒ Base del Informe
- II. ☐ Prioridad
- III. ☒ El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación Industrial
- IV. ☐ Falta de unidad de invención
- V. ☒ Declaración motivada bajo el Art. 35(2) con relación a la novedad, nivel inventivo o aplicación Industrial; citaciones y explicaciones que soportan dicha declaración
- VI. ☐ Ciertos documentos citados
- VII. ☐ Ciertos defectos en la solicitud internacional
- VIII. ☐ Ciertas observaciones en la solicitud internacional

Fecha de presentación de la demanda 31/07/2002	Fecha en que se completó este informe 22.08.2002
Nombre y dirección de la autoridad encargada del examen preliminar internacional: Oficina de Patentes Europea, Gitschiner Str. 103 D-10989 Berlin - Alemania Tel. +49 30 25901-0 Fax: +49 30 25901-840	Oficial autorizado DE BUNDEL E. R. J. Teléfono: +49 89 2399 2828

**INFORME DEL EXAMEN
PRELIMINAR INTERNACIONAL**Solicitud internacional No. PCT/EP02/01249

I. BASE DEL INFORME

La base de este examen preliminar Internacional es la solicitud de patente como fue presentada originalmente.

III. El no establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación industrial

El interrogante sobre si la invención reivindicada parece ser novedosa, constituir un nivel inventivo o tener aplicación industrial no ha sido el objeto del examen preliminar Internacional con referencia a las reivindicaciones sobre las cuales no se ha realizado una búsqueda (Artículo 17(2) (a) o (3) y Regla 66.1(e) PCT); ver también el reporte de búsqueda Internacional).

V. Declaración motivada bajo la Regla 66.2 (a)(II) en relación a la novedad, nivel inventivo o aplicación industrial.

Hasta el alcance en que se realizó el examen preliminar Internacional (ver ítem III arriba), se destaca lo siguiente:

A la luz de los documentos citados en el reporte de búsqueda internacional se considera que la invención, como fue definida en las reivindicaciones independientes, las cuales fueron el objeto de un reporte de búsqueda internacional, cumplen con los criterios mencionados en el Artículo 33(1) PCT, es decir, parece ser novedosa, constituir un nivel inventivo y tener aplicación industrial.

Forma de Patentes 1/77

(Emblema)

(Logotipo) | Error! Marcador no definido.

INVERSIONISTA EN LA GENTE

LA OFICINA DE PATENTES

La Oficina de Patentes

Concept House

Cardiff Road

Newport

Gales del Sur

NP10 8QQ

Yo, el suscrito, siendo un funcionario debidamente autorizado de acuerdo con la Sección 74(1) y (4) de la Ley de Desregulación y Contratación Externa de 1994, para firmar y expedir certificados a nombre del Contralor General, mediante la presente certifico que el anexo es una copia fiel de los documentos tal como se presentaron originalmente en relación con la Solicitud de Patente identificada en los mismos.

De acuerdo con las Reglas de Patentes (Re-registro de Sociedades) de 1982, si una sociedad nombrada en este certificado y en cualesquiera documentos acompañantes, se ha re-registrado, de acuerdo con la Ley de Sociedades de 1980, con el mismo nombre que aquél con el que se registró

Forma de Patentes 1/77

inmediatamente antes del re-registro, salvo por la sustitución como, o la inclusión como, la última parte del nombre con las palabras "sociedad pública limitada" o sus equivalentes en Galo, las referencias al nombre de la sociedad en este certificado y en cualesquiera documentos acompañantes, se tratarán como referencias al nombre con el cual así se re-registró.

De acuerdo con las reglas, las palabras "sociedad pública limitada" pueden ser reemplazadas por s.p.l., spl, S.P.L., ó SPL.

El re-registro según la Ley de Sociedades no constituye una nueva entidad legal, sino que meramente sujeta a la sociedad a ciertas reglas adicionales de la ley de sociedades.

Firma: (Firmado)

Fecha: 29 de enero de 2002

(Aparece un sello móvil de la Oficina de Patentes).

1/77

08FEB01 E604188-3 DO0524

P01/7700.0 00-0103046.9

Ley de Patentes de 1977

(Regla 16)

(Aparece un sello ovalado impreso con la siguiente leyenda:

LA OFICINA DE PATENTES
07 DE FEBRERO DE 2001
RECIBIDO PERSONALMENTE).

LA OFICINA DE PATENTES

La Oficina de Patentes

Cardiff Road

Newport

Gwent NP10 8QQ

SOLICITUD PARA LA CONCESION DE UNA PATENTE

(Ver las notas al reverso de esta forma. También puede obtener un folleto de explicaciones en la Oficina de Patentes, para ayudarle a llenar esta forma).

1. Su referencia: **4-31862P1**

Forma de Patentes 1/77

2. Número de Solicitud de Patente: ..
(La Oficina de Patentes llenará esta parte)

0103046.9

07 DE FEBRERO DE 2001
3. Nombre completo, domicilio, y código postal de cada
solicitante (subraye todos los apellidos):

NOVARTIS AG
SCHWARZWALDALLEE 215
4058 BASILEA
SUIZA

- Número ADP de Patentes (si lo conoce):
- 7194566001**
- Si el solicitante es un cuerpo corporativo, dé el país/estado
de su incorporación:

SUIZA

4. Título de la invención:
Compuestos Orgánicos

5. Nombre de su agente (si tiene alguno):
B. A. YORKE & CO.
AGENTES DE PATENTES AUTORIZADOS

"Dirección para notificaciones" en el Reino Unido, a donde se debe enviar toda la correspondencia (incluyendo el

código postal):

COOMB HOUSE, 7 ST. JOHN'S ROAD
ISLEWORTH
MIDDLESEX TW7 6NH

Número ADP de Patentes *(si lo conoce):*

1800001

6. Si está declarando prioridad a partir de una o más solicitudes de patente anteriores, dé el país y la fecha de presentación de cada una de estas solicitudes anteriores, y *(si lo conoce)* cada número de solicitud:

País: - - -

Número de solicitud de prioridad *(si lo sabe):* - - -

Fecha de presentación (día/mes/año): - - -

7. Si esta solicitud está dividida o se deriva de otra manera de una solicitud anterior del Reino Unido, dé el número y la fecha de presentación de la solicitud anterior:

Número de solicitud anterior: - - -

Fecha de presentación (día/mes/año): - - -

8. Es una declaración de invención y del derecho de otorgar una patente requerida en apoyo de esta

37

- Ver la nota (d)):** **Si**

Páginas de continuación de esta forma	--
Descripción	11
Reivindicaciones	2
Resumen	1
Dibujo(s)	--

- Documentos de prioridad: --
- Traducción de documentos de prioridad: --

Forma de Patentes 1/77

Declaración de invención y derecho a la concesión de una
patente (Forma de Patentes 7/77): --

Solicitud de examen preliminar y búsqueda (Forma de Patentes
9/77): UNA

Solicitud de examen sustantivo (Forma de Patentes 10/77): --

Cualesquiera otros documentos (por favor especifique):

11. Solicitamos la concesión de una patente con base en
esta solicitud.

Firma: B. A. Yorke & Co.

(Firmado)

Fecha: 07 de febrero de 2001

12. Nombre y número telefónico diurno de la persona para
hacer contacto en el Reino Unido:

SRA. E. CHEETHAM

020 8560 5847

Advertencia

Después de que se haya presentado una solicitud de
patente, el Contralor de la Oficina de Patentes considerará si
se debe prohibir o restringir la publicación o comunicación de
la invención, de acuerdo con la Sección 22 de la Ley de
Patentes de 1977. Se le informará si es necesario prohibir o
restringir su invención de esta manera. Además, si usted vive

Forma de Patentes 1/77

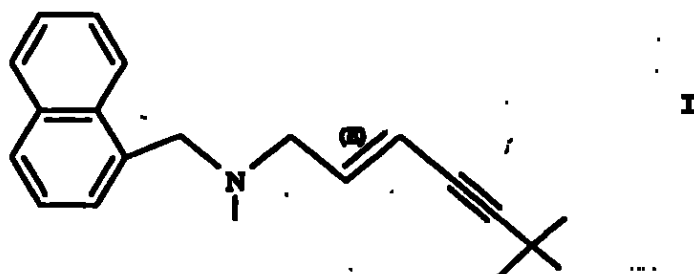
en el Reino Unido, la Sección 23 de la Ley de Patentes de 1977 le impide solicitar una patente en el extranjero sin obtener primero un permiso por escrito de la Oficina de Patentes, a menos que se haya presentado una solicitud cuando menos 6 semanas antes en el Reino Unido para una patente para la misma invención, y no se hayan dado instrucciones que prohíban la publicación o la comunicación, o se hayan revocado dichas instrucciones.

Notas

- a) Si necesita ayuda para llenar esta forma, o tiene alguna pregunta, por favor haga contacto con la Oficina de Patentes al 0645 500505.
- b) Escriba sus respuestas en letras mayúsculas, utilizando tinta negra, o puede mecanografiarlas.
- c) Si no hay suficiente espacio para todos los detalles pertinentes en cualquier parte de esta forma, por favor continúe en una hoja de papel separada, y escriba "ver página de continuación" en las partes pertinentes. Cualquier página de continuación se debe adjuntar a esta forma.
- d) Una vez que haya llenado la forma, debe recordar firmarla y fecharla.
- e) Para los detalles de los derechos y de las maneras de pagar, por favor haga contacto con la Oficina de Patentes.

REIVINDICACIONES

1. Una sal del compuesto de la fórmula I:



con ácido málico,

es decir, (E)-N-metil-6,6-dimetil-N-(1-naftilmetil) hept-2-en-4-inil-1-amina en una forma de sal de adición de ácido málico.

2. Un compuesto de acuerdo con la reivindicación 1, en la forma del malato de L-(-)-hidrógeno.

3. Un proceso, el cual comprende hacer reaccionar el compuesto de la fórmula I en forma de base libre, con una forma de ácido málico apropiada, y recuperar de la mezcla de reacción el compuesto de acuerdo con la reivindicación 1 resultante.

4. Una composición farmacéutica que comprende un compuesto de acuerdo con la reivindicación 1, junto con cuando menos un vehículo o diluyente farmacéuticamente aceptable.

5. Una composición farmacéutica, siempre que se

prepare a partir de un compuesto de acuerdo con la reivindicación 1.

6. Un compuesto de acuerdo con la reivindicación 1, para utilizarse como un producto farmacéutico.

7. Un compuesto de acuerdo con la reivindicación 1, para utilizarse en la preparación de un medicamento.

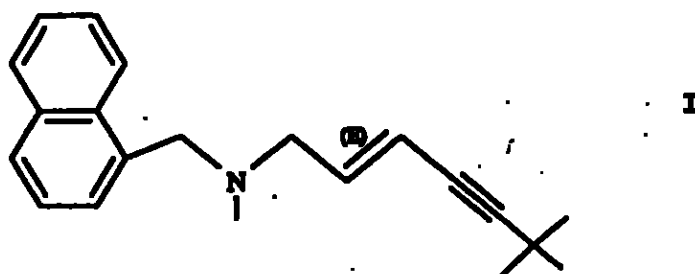
8. Un compuesto de acuerdo con la reivindicación 1, siempre que se prepare mediante un proceso de acuerdo con la reivindicación 3.

9. El compuesto de la fórmula I, en forma de base libre o en forma de sal diferente de una forma de sal de adición de ácido málico, siempre que se prepare a partir de un compuesto de acuerdo con la reivindicación 1.

10. El uso de un compuesto de acuerdo con la reivindicación 1, en la preparación de un medicamento para el tratamiento, especialmente oral, de enfermedades susceptibles a terapia con el compuesto de la fórmula I en forma de base libre o en forma de sal, tales como enfermedades fúngicas.

RESUMEN

La invención se refiere a sales del compuesto de la fórmula I:



con ácido málico,

es decir, (E)-N-metil-6,6-dimetil-N-(1-naftilmetil) hept-2-en-4-inil-1-amina en una forma de sal de adición de ácido málico.

* * * * *

Yo, ANA ELENA FERRER RAMÍREZ, Perita Traductora Autorizada por el Tribunal Superior de Justicia del D.F., y miembro de la Organización Mexicana de Traductores, A.C., con domicilio en Av. Clavería 224-205, Col. Clavería, México, D.F. 02080, Tels. 5396 2669 y 5396 5201, certifico que el documento precedente es, a mi leal saber y entender, una traducción fiel y exacta del documento original en idioma inglés que tuve a la vista.

México, D. F., 5 de agosto de 2003

ANA ELENA FERRER R.
Perita Traductora
Autorizada por el Tribunal
Superior de Justicia del D.F.

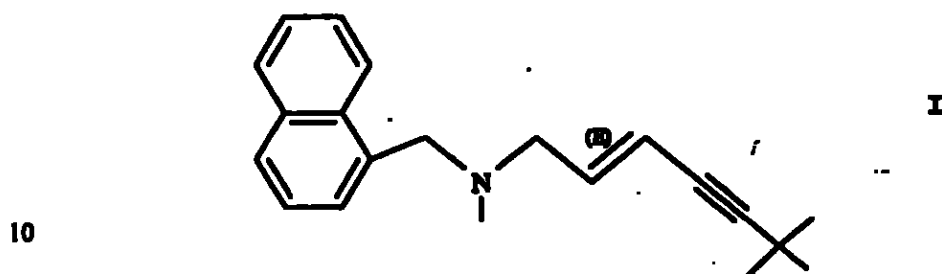
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Ana Elena Ferrer Ramírez

SALES DE ADICIÓN DE ÁCIDO MÁLICO DE TERBINAFINA

La invención se refiere a sales de adición de ácido de antimicóticos de alilamina.

5 Se refiere a sales del compuesto de la fórmula I:



con ácido málico,

es decir, (E)-N-metil-6,6-dimetil-N-(1-naftilmetil) hept-2-en-4-yn-1-amina en una forma de sal de adición de
15 ácido málico,

denominados brevemente más adelante en la presente como "los compuestos de la invención".

Los compuestos de la invención son novedosos, y son sales farmacéuticas mejoradas del compuesto conocido de la
20 fórmula I.

Un compuesto de la invención está en una forma racémica o enantiomérica. Está en una forma de sal de adición de ácido de malato o de malato de hidrógeno, de preferencia de malato de hidrógeno. La fracción de ácido málico de
25 preferencia está en una forma racémica DL-(+)- ó L-(-)-

enantiomérica, en especial en una forma L-(-)-enantiomérica. Por consiguiente, se prefiere en particular el malato de DL-(+)- ó y L-(-)-, en especial L-(-)-hidrógeno.

Los compuestos de la invención exhiben
5 polimorfismo. La invención incluye a los compuestos de la invención en cualquier forma polimórfica, por ejemplo la forma A o la forma B del malato de L-(-)-hidrógeno como se describe más adelante en la presente.

La invención también incluye un proceso para la
10 preparación de un compuesto de la invención, el cual comprende hacer reaccionar un compuesto de la fórmula I en forma de base libre, con una forma de ácido málico apropiada, y recuperar de la mezcla de reacción la sal resultante.

El proceso de la invención se puede efectuar de una
15 manera convencional, por ejemplo mediante una reacción en un solvente inerte apropiado, tal como isopropanol, etiléster del ácido acético, acetato de isopropilo, ciclopentanona, butanol normal, o formato de etilo.

El compuesto de la fórmula I en la forma de sal de
20 adición de ácido clorhídrico y su uso como un antimicótico, por ejemplo en el tratamiento de micosis causada por infección por dermatofitos, se conoce, entre otros, de la Patente Europea Número EP 24687 y sus equivalentes. Está disponible en una forma de base libre o de sal de adición de
25 ácido clorhídrico bajo la marca comercial registrada

Lamisil®, con el nombre genérico de terbinafina. También se han/ mencionado en la literatura dos formas de sal adicionales, por ejemplo en la Patente Europea Número EP 515310A1, el lactato y el ascorbato, en relación con
5 composiciones farmacéuticas para aplicación tópica a la piel.

La terbinafina es un agente antifúngico oralmente y tópicamente efectivo. Es efectivo en un amplio rango de enfermedades fúngicas, incluyendo, entre otras, infección de senusitis fúngica, y onicomycosis. Es particularmente útil
10 contra dermatofitos, hongos contagiosos que invaden los tejidos muertos de la piel o sus apéndices tales como el estrato córneo, las uñas, y el pelo. Este hongo de las uñas hace su hogar en el lecho de la uña, protegido por la uña externa dura. Por consiguiente, una vez que se establece la
15 infección debajo de la uña, la uña misma proporciona al hongo un medio ambiente protegido que le permite crecer. Los efectos de estos hongos sobre las uñas pueden ser desagradables, complican seriamente el cuidado de los pies, tienen un impacto perjudicial sobre la calidad de vida y
20 bienestar global del paciente, y perjudican la capacidad del paciente para trabajar. Si se dejan sin tratar, los hongos pueden deformar las uñas de los pies de una manera permanente, y conducen a dolor al caminar. Adicionalmente, los hongos pueden conducir a fisuras en la piel, que alientan
25 las infecciones bacterianas. Se pueden presentar serias

complicaciones como un resultado de estas infecciones en las personas que sufren de diabetes, tales como síndrome de pie diabético, incluyendo complicaciones relacionadas con la enfermedad primaria, por ejemplo gangrena, que, finalmente, pueden ser amenazantes de la vida o requieren de amputación. Otros subgrupos de pacientes de alto riesgo incluyen los pacientes infectados con el virus de inmunodeficiencia humana (VIH), los pacientes con el síndrome e inmunodeficiencia adquirida (SIDA), y los pacientes con otros tipos de inmunosupresión (por ejemplo, receptores de trasplante y pacientes con terapia de corticosteroides a largo plazo). Existe una prevalencia incrementada de onicomycosis en los ancianos (hasta el 30 por ciento a los 60 años de edad). Los hongos comúnmente involucrados son *Microsporum*, *Trichophyton*, tales como *Trichophyton rubrum* o *Trichophyton mentagrophytes*, y *Epidermophyton* tales como *Epidermophyton floccosum*. A través de las disciplinas médicas, la onicomycosis es bien reconocida como ardua tanto para diagnosticar como manejar, en particular en los ancianos.

La terbinafina también es útil para tratar la onicomycosis de las uñas de los pies y de las manos (por ejemplo, *Tinea unguium*) debido a dermatofitos. En realidad, la terbinafina ha abierto el tratamiento para *Tinea unguium* causada por *Trichophyton*. Por ejemplo, se ha mencionado que el tratamiento de las uñas de los pies debe desalentarse con

la griseofulvina estándar previamente utilizada, debido a que se requiere un tratamiento de 1 a 2 años, a que es usual la recurrencia, y es poco probable una cura completa.

Para el uso oral en onicomycosis, normalmente se
5 administra clorhidrato de terbinafina como una forma de
tableta de liberación inmediata que contiene 250 miligramos
de terbinafina una vez al día. Esta tableta, vendida bajo la
marca comercial registrada Lamisil[®], libera terbinafina hasta
el grado del 80 por ciento durante un período de 30 minutos,
10 medido mediante estudios de disolución *in vitro*
convencionales, por ejemplo a un pH de 3 utilizando el método
de paleta. Se requiere un tratamiento con terbinafina durante
12 semanas. El progreso de su efectividad clínica se ve con
el crecimiento de la uña sana, que empuja hacia afuera y
15 reemplaza la desagradable uña enferma que contiene suciedad y
hongo muerto. Se necesitan aproximadamente 10 meses para que
se forme una uña del pie totalmente nueva.

Aunque en general se considera que la terbinafina
es segura como cualquier fármaco de prescripción, se han
20 reportado eventos adversos asociados con su uso. Ha habido un
número de eventos adversos registrados, por ejemplo dolores
de cabeza, síntomas gastrointestinales (incluyendo diarrea,
dispepsia, dolor abdominal, náusea, y flatulencia),
anormalidades de las pruebas de hígado, por ejemplo
25 anormalidades enzimáticas, síntomas dermatológicos tales como

pruritis, urticaria y comezón, y alteraciones del sabor, por ejemplo pérdida del sabor. Estos eventos adversos son en general leves y transitorios. Otros eventos adversos incluyen disfunción hepatobiliar idiosincrática sintomática (por ejemplo, hepatitis colestática), reacciones severas de la piel tales como síndrome de Stevens-Johnson, neutropenia, y trombocitopenia. Todavía otros eventos adversos pueden incluir alteraciones visuales, tales como cambios en el lente ocular y en la retina, así como reacciones alérgicas incluyendo anafilaxis, fatiga, vómito, artralgia, mialgia, y pérdida del cabello. La terbinafina es un potente inhibidor de CYP2D6, y puede ocasionar interacciones clínicamente significativas cuando se coadministra con sustratos de esta isoforma, tales como nortriptilina, desipramina, perfenazina, metoprolol, encainida, y propafenona. Posteriormente en la presente, cualquiera y todos estos eventos son referidos brevemente como Eventos Adversos.

Se conocen las propiedades farmacocinéticas y biofarmacéuticas del clorhidrato de terbinafina. Por lo tanto, es bien absorbido. En sujetos humanos, aparecen concentraciones en plasma pico del fármaco (posteriormente en la presente, C_{max}) de aproximadamente 1.3 microgramos/mililitro (con una variación de aproximadamente el 20 por ciento, por ejemplo de 0.9 a 1.6 microgramos/mililitro) dentro de 1 a 2 horas después de la

administración de una sola dosis de 250 miligramos de terbinafina. El área debajo de la curva durante 24 horas (posteriormente en la presente, AUC) es de aproximadamente 4.76 microgramos.hora/mililitro. El incremento en el AUC es del 42 por ciento cuando se administra terbinafina con un alimento rico en grasa. En los pacientes con insuficiencia renal (por ejemplo, liberación de creatinina $\geq$ 50 mililitros/minuto) o con cirrosis hepática, la liberación de terbinafina se reduce por aproximadamente el 50 por ciento.

En el estado continuo, por ejemplo cuando los valles y picos son constantes después de una dosificación de varios días, en comparación con una sola dosis, C_{max} es 25 por ciento más alta, y AUC se incrementa por un factor de 2.5. Esto es consistente con una vida media efectiva para la terbinafina de aproximadamente 36 horas.

Se han dado a conocer las propiedades farmacocinéticas y de absorción, por ejemplo, en J. Faergemann y colaboradores, Acta Derm. Venereol. (Stockh.) 77 (1997) 74-76. Sin embargo, no se conoce el sitio de absorción de la terbinafina, y no hay una correlación clínicamente probada del efecto con el perfil farmacocinético, de modo que no hay un punto de partida racional para desarrollar formas farmacéuticas que contengan terbinafina con mejores efectos terapéuticos.

A pesar de la muy grande contribución que ha hecho

la terbinafina, la presentación reportada de Eventos Adversos indeseables ha sido un impedimento para su uso oral o aplicación más amplia. Las dificultades particulares encontradas en relación con la dosificación oral con el
5 clorhidrato de terbinafina han conducido inevitablemente a restricciones en el uso de la terapia con terbinafina para el tratamiento de condiciones de enfermedad relativamente menos severas o peligrosas, por ejemplo *Tinea pedis*.

Ahora se ha encontrado que, de una manera
10 inesperada, las sales del compuesto de la fórmula I con ácido málico poseen propiedades farmacocinéticas particularmente benéficas, y se ha encontrado además que poseen una combinación única de propiedades de formulación favorables que pueden hacerlas particularmente adecuadas para la
15 preparación de composiciones farmacéuticas de terbinafina, adaptadas para administración sistémica y tópica.

Por consiguiente, la variabilidad de los parámetros farmacocinéticos es considerablemente menor cuando se emplea sistémicamente una sal de malato del compuesto de la fórmula
20 I, que con las sales conocidas o la base libre, por ejemplo el clorhidrato.

Esto aparece, entre otros, de un estudio farmacocinético en animales que involucró a 7 perros Beagle que pesaban aproximadamente 10 kilogramos, con una edad de
25 aproximadamente 5 años, después de la administración oral de

cápsulas preparadas mezclando una sustancia de sal de terbinafina activa [clorhidrato o malato de L-(-)-hidrógeno; 62.5 miligramos de equivalente de base por cápsula] con lactosa en una proporción de 1:1 en peso/peso, y llenándose en cápsulas de gelatina dura apropiadas (distribución de tamaños de partículas similar para ambas sales).

La variabilidad inter-animales en la exposición de terbinafina al plasma (como se expresa por el coeficiente de variación [posteriormente en la presente CV] del área debajo de la curva [AUC]), se ha encontrado que se reduce distintivamente cuando se administra la sal de malato de L-(-)-hidrógeno de terbinafina, es decir, por un 30 por ciento, comparándose con el 39 por ciento con el clorhidrato. Los valores AUC medios obtenidos de esta manera fueron, respectivamente, de 392 y 348 nanogramos.hora/mililitro, mostrando inclusive un ligero incremento en la exposición del plasma absoluto con la sal de malato de hidrógeno.

Los valores C_{max} medios obtenidos mediante lo mismo son de 134 y 146 nanogramos/mililitro para el malato de L-(-)-hidrógeno y el clorhidrato, respectivamente, con valores CV correspondientes del 26 por ciento y del 47 por ciento, respectivamente, una indicación adicional de la variabilidad reducida de los parámetros farmacocinéticos cuando se utiliza una sal de malato.

Se puede esperar de lo mismo que, en sujetos

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humanos, se obtenga una variabilidad similarmente reducida de los parámetros farmacocinéticos, y por consiguiente, se puede prever una eficacia todavía más estable del tratamiento con terbinafina en las indicaciones antimicóticas, inclusive en
5 dosificaciones muy altas, en particular sobre su administración oral, por ejemplo en el tratamiento oral de onicomycosis.

Además, los compuestos de la invención también se pueden emplear tópicamente, por ejemplo sobre la uña, como se
10 puede ver, por ejemplo, del siguiente ensayo de penetración/permeación *in vitro*:

se utilizan uñas de pie cadavérico humano en una celda de Franz (Figura 1) modificada para aceptar uñas de pie humano cadavérico, al tener un par de anillos flexibles
15 hechos de un elastómero de silicona (PDMS) que tiene buenas propiedades selladoras para montar adecuadamente las uñas duras, utilizando conteo de cintilación de líquidos (LCS) (límite de detección en picogramos) para medir el incremento en la radioactividad en el compartimiento aceptor. Cada
20 medición se efectúa por triplicado. Se exponen 90 uñas aleatoriamente seleccionadas durante 72 horas a una solución de 100 microlitros de clorhidrato de terbinafina o malato de L-(-)-hidrógeno de terbinafina marcados con ^{14}C (forma A) [25 $\mu\text{Bq/ml}$; 1 por ciento de producto activo; 5 por ciento de 1,2-propilenglicol; 2 por ciento de Cetomacrogol-1000^R
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(polioxietilenglicol-1000-monoacetiléter); 25 por ciento de etanol al 94 por ciento; 67 por ciento de agua destilada] (peso/peso). Cada área de la uña expuesta a la formulación tiene 9 milímetros de diámetro (aproximadamente 64 milímetros cuadrados). La exposición se efectúa bajo condiciones oclusivas (cámara cerrada al aire) y no oclusivas (cámara abierta al aire).

El producto radiomarcado es detectable en la cámara receptora llenada con regulador desde aproximadamente 8 horas de incubación. Su concentración en la cámara receptora, medida mediante LSC, se incrementa con el tiempo de incubación y con la concentración de la formulación aplicada. Se utilizan un total de 24 cámaras de penetración en paralelo. Cada formulación se mide por triplicado.

El resultado es como aparece en la Figura 2: bajo condiciones tanto oclusivas (puntos negros) como no oclusivas (cuadros negros), se observa una permeación sustancial a las 72 horas (aproximadamente 63 nanogramos y 41 nanogramos, respectivamente).

Además, se ha encontrado que los compuestos de la invención poseen de una manera sorprendente, propiedades de formulación favorables. Por consiguiente, forman cristales más fácilmente que el clorhidrato o la base libre. Además, los cristales de, por ejemplo, la sal de malato de L-(-)-hidrógeno, exhiben diferentes formas polimórficas. Los

polimorfos tienen diferentes velocidades de disolución, comportamiento de molienda y estabilidad, por ejemplo en formas galénicas en donde el compuesto farmacéuticamente activo está en una forma sólida, tal como tabletas o suspensiones, y tienen influencia sobre la biodisponibilidad. Por consiguiente, la presencia sorprendente del polimorfismo es conveniente en términos de una mejor procesabilidad, tal como con el polimorfo particularmente estable termodinámicamente, en formulaciones con el compuesto en forma sólida, por ejemplo tabletas o suspensiones, o teniendo el polimorfo una velocidad de disolución o solubilidad particularmente alta, en formulaciones con el compuesto disuelto, por ejemplo barnices para uñas. Los compuestos de la invención, por consiguiente, son mejor procesables para, por ejemplo, la formulación de tabletas a gran escala; también tienen propiedades de penetración/permeación favorables, y por lo tanto, se pueden formular fácilmente en formas tópicas, tales como barnices para uñas. Adicionalmente, poseen una buena solubilidad en agua y muchos solventes orgánicos, un requisito previo para una buena biodisponibilidad: por consiguiente, a 25°C, el malato de L-(-)-hidrógeno es soluble hasta aproximadamente 12-15 miligramos/mililitro en agua, y >30 miligramos/mililitro en acetato de etilo, comparándose con 6.7 miligramos/mililitro en agua, y 0.7 miligramos/mililitro en acetato de etilo para

el clorhidrato. Además, no son higroscópicos, proporcionando de esta manera formulaciones estables, mientras que minimizan el riesgo de una descomposición química intrínseca.

Por consiguiente, muestran una combinación única de
5 buena procesabilidad, buena solubilidad, y no higroscopicidad, que los hace notoriamente adecuados para la preparación de composiciones farmacéuticas de terbinafina.

La invención además incluye:

- una composición farmacéutica que comprende un
10 compuesto de la invención, junto con cuando menos un vehículo o diluyente farmacéuticamente aceptable;

- una composición farmacéutica que comprende al compuesto de la fórmula I en forma libre o en forma de sal farmacéuticamente aceptable diferente de una forma de sal de
15 adición de ácido málico, siempre que se prepare a partir de un compuesto de la invención;

- un compuesto de la invención para utilizarse como un producto farmacéutico;

- un compuesto de la invención para utilizarse
20 en la preparación de un medicamento;

- un compuesto de la invención siempre que se prepare mediante un proceso como se define anteriormente;

- un compuesto de la fórmula I en forma de base libre o en forma de sal diferente de una forma de sal de
25 adición de ácido málico, siempre que se prepare a partir de

un compuesto de la invención;

- el uso de un compuesto de la invención en la preparación de un medicamento para el tratamiento, por ejemplo oralmente, de enfermedades susceptibles a terapia con
5 el compuesto de la fórmula I en forma de base libre o en forma de sal, tales como enfermedades fúngicas;

- un proceso para la preparación de una composición farmacéutica, el cual comprende mezclar un compuesto de la invención, junto con cuando menos un vehículo
10 o diluyente farmacéuticamente aceptable; y

- un método para el tratamiento profiláctico o curativo de enfermedades fúngicas, tales como infección de senusitis fúngicas u onicomycosis, el cual comprende la administración de una cantidad terapéuticamente efectiva de un compuesto de
15 la invención a un sujeto que necesite dicho tratamiento.

Las composiciones farmacéuticas que incorporan un compuesto de la invención, de preferencia se componen en una forma de dosificación unitaria, por ejemplo llenándose en cubiertas de cápsulas, por ejemplo cubiertas de cápsulas de
20 gelatina blanda o dura, o formando tabletas, o con algún otro proceso de moldeo. Por consiguiente, las formas de dosificación unitaria adecuadas para administrarse una o dos veces al día, por ejemplo, dependiendo del propósito particular de la terapia, la fase de la terapia, etcétera,
25 apropiadamente comprenderán la mitad o la dosis diaria total

contemplada. Estas composiciones se pueden administrar dos o tres veces a la semana. De preferencia, las composiciones se administran una vez al día.

La cantidad de compuesto de la invención, por supuesto, variará, por ejemplo, dependiendo de hasta qué grado están presentes otros componentes, del modo de administración, y del tratamiento deseado. Sin embargo, en general estará presente en una cantidad dentro del rango de aproximadamente el 0.1 por ciento a aproximadamente el 35 por ciento en peso, basándose en el peso total de la composición. La dosificación diaria total del compuesto activo (expresada en equivalente de base libre) es, por ejemplo, de aproximadamente 50 miligramos a aproximadamente 500 miligramos al día, por ejemplo 250 miligramos al día, o 400 miligramos, 600 miligramos ó 700 miligramos al día, convenientemente dados, por ejemplo, en dosis divididas hasta cuatro veces al día. Las formas de dosificación unitaria comprenden, por ejemplo, de aproximadamente 12.5 miligramos a aproximadamente 800 miligramos del compuesto de la invención (expresados en equivalente de base libre) mezclados con cuando menos un vehículo o diluyente sólido o líquido farmacéuticamente aceptable.

Los compuestos de la invención se pueden administrar de una manera similar a los estándares conocidos para utilizarse en tales indicaciones.

Se pueden mezclar con vehículos o diluyentes quimioterapéuticamente aceptables convencionales, y opcionalmente excipientes adicionales, y se pueden administrar, por ejemplo, oralmente, por ejemplo en la forma de formulaciones, tales como tabletas y cápsulas. Una formulación de tableta preferida incluye un compuesto de la invención, un auxiliar de compresión tal como celulosa microcristalina, un aditivo para proporcionar brillo a la tableta, tal como fosfato de calcio dibásico anhidro, un desintegrante tal como glicolato de almidón de sodio, y un lubricante tal como estearato de magnesio. Una formulación de cápsula preferida incluye un compuesto de la invención, un diluyente inerte, un desintegrante seco, y un lubricante, como se describe anteriormente.

De una manera alternativa, se pueden administrar tópicamente, por ejemplo en la forma de formulaciones, por ejemplo lociones, soluciones, ungüentos o cremas, tales como barnices de uñas, o parenteralmente o intravenosamente. La concentración de la sustancia activa, por supuesto, variará, por ejemplo, dependiendo del compuesto de la invención empleado, del tratamiento deseado, y de la naturaleza de la forma o formulación utilizada. En general, se obtienen resultados satisfactorios, por ejemplo, en formulaciones tópicas, en concentraciones de aproximadamente el 0.1 por ciento a aproximadamente el 10 por ciento, en particular de

aproximadamente el 0.1 por ciento a aproximadamente el 2 por ciento, en especial aproximadamente el 1 por ciento en peso.

Por consiguiente, con la presente invención también se proporcionan composiciones de terbinafina novedosas que
5 contienen a los compuestos de la invención que satisfacen o reducen sustancialmente las dificultades en la terapia con terbinafina encontradas hasta ahora. En particular, pueden contener terbinafina en concentraciones suficientemente
10 altas y constantes para permitir una administración oral conveniente una vez al día, mientras que al mismo tiempo se logra la mejor seguridad y tolerabilidad en términos de menos Eventos Adversos.

Por consiguiente, la presente invención hace posible la reducción de los tiempos de tratamiento con
15 terbinafina requeridos para lograr una terapia efectiva, reduciendo el tiempo de exposición a la terbinafina, y mejorando el perfil de seguridad global. En adición, permite hacer una estandarización más cercana, así como una optimización de los requerimientos de dosificación diaria
20 continua para los sujetos individuales que reciban terapia con terbinafina, así como para grupos de pacientes que se sometan a una terapia equivalente. Mediante una estandarización más cercana de los regímenes terapéuticos de los pacientes individuales, se pueden reducir los parámetros
25 de dosificación para grupos de pacientes particulares, así

como los requerimientos de monitoreo, reduciendo de esta manera sustancialmente el costo de la terapia.

Otras propiedades farmacocinéticas de las composiciones farmacéuticas que contienen a los compuestos de la invención se pueden determinar en estudios farmacológicos animales y humanos convencionales (biodisponibilidad). Por ejemplo, se puede llevar a cabo un estudio farmacológico convencional en voluntarios no fumadores masculinos o femeninos sanos con edades entre 18 y 45 años que estén dentro del 20 por ciento del peso corporal ideal. El estudio puede ser una aplicación cruzada de una sola dosis. Los sujetos se internan durante 24 horas. Se toman muestras de sangre a las 1, 2, 4, 8, 16, 32, y 72 horas después de la administración de una composición farmacéutica que contenga a un compuesto de la invención, y se prueban para determinar la terbinafina. Las concentraciones de terbinafina en sangre o en plasma se pueden determinar de una manera convencional, por ejemplo mediante técnicas analíticas de HPLC/UV ó LC-MS. La seguridad se juzga de acuerdo con una lista de verificación estándar basada en los síntomas de Eventos Adversos después de una semana. De preferencia, la dosis de sal de terbinafina es de 400, 600, ó 700-800 miligramos de equivalente de base al día. La seguridad de la terbinafina en esta dosis sobre la corta duración del tratamiento es notoria. Las composiciones orales de la invención de

preferencia exhiben una C_{max} del 100-250 por ciento, por ejemplo del 100-150 por ciento de la mostrada con 250 miligramos de tabletas de clorhidrato de terbinafina de liberación inmediata, por ejemplo administradas como una sola
5 dosis y/o en el estado continuo, por ejemplo una vez al día durante 7 días.

Se pueden llevar a cabo estudios farmacocinéticos de concentración del fármaco en la piel y en las uñas de acuerdo con los mismos principios estipulados para los
10 estudios farmacológicos convencionales anteriormente mencionados. Por ejemplo, se puede efectuar un estudio clínico con una dosificación diaria de las composiciones que contengan a un compuesto de la invención durante un período de tratamiento de tres semanas.

15 Las tabletas que contienen a los compuestos de la invención son útiles para las mismas indicaciones que las tabletas de clorhidrato de terbinafina de liberación inmediata conocidas. La utilidad de los compuestos de la invención se puede observar en pruebas clínicas
20 convencionales o en modelos animales convencionales. Por ejemplo, se pueden aseverar las dosificaciones de las composiciones que contienen a un compuesto de la invención, que den una AUC de niveles en plasma de terbinafina equivalente a una AUC de los niveles en plasma que den un
25 efecto terapéutico sobre la administración de las formas de

dosificación oral de clorhidrato de terbinafina conocidas, por ejemplo una tableta. Las composiciones farmacéuticas que contienen a un compuesto de la invención son particularmente y sorprendentemente bien toleradas con respecto a los Eventos Adversos mencionados anteriormente, provocan menos Eventos Adversos cuando se co-administran con sustratos de CYP2D6 tales como nortriptilina, desipramina, perfenazina, metoprolol, encainida, y propafenona.

Se puede efectuar un estudio doble-ciego controlado por positivo y controlado por placebo, aleatoriamente seleccionado, por ejemplo, con sujetos que tengan onicomycosis de la uña del pie confirmada mediante microscopio y cultivo. El tratamiento se lleva a cabo durante 12 semanas. Se pueden efectuar ensayos clínicos en varios cientos de pacientes para aseverar la exención de Eventos Adversos. Sin embargo, ya se puede mostrar la eficacia terapéutica en estudios con 25 pacientes con edades mayores de 12 años. La seguridad se evalúa mediante un reporte de Evento Adverso de los aspectos clínicos y los signos vitales. La eficacia se determina mediante microscopio, procedimientos de cultivo, y observación visual de los signos y síntomas. La eficacia se ve en los pacientes con los hongos descritos anteriormente, en especial *Trichophyton rubrum*, *Trichophyton mentagrophytes*, y *Epidermophyton floccosum*. Los pacientes incluyen aquéllos con factores de predisposición, tales como

circulación sanguínea deteriorada, neuropatía periférica, diabetes mellitus, daño por trauma menor repetido, y defectos inmunes limitados, así como SIDA. Los pacientes tienen (i) onicomycosis subungual lateral distal, empezando en el
5 hiponiquio y extendiéndose próximamente al lecho y la matriz de la uña, (ii) onicomycosis subungual proximal, en donde el hongo infecta la cutícula y el eponiquio para llegar a la matriz, en donde llega a encerrarse en la sustancia de la placa de la uña, (iii) onicomycosis distrófica total, y (iv)
10 onicomycosis blanca superficial. Si se desea, se pueden evaluar las concentraciones en plasma de terbinafina de una manera convencional, o como se describe en la presente. Las concentraciones de terbinafina en la uña se pueden evaluar de un pedazo de uña seguido por análisis.

15

Explicación de las Figuras:

Figura 1: representación esquemática de una célula de Franz.

Figura 2: ensayo de penetración/permeación:
20 cantidad recuperada en la cámara receptora (en nanogramos) contra el tiempo (en horas) con una solución al 1 por ciento de malato de (L)-(-)-hidrógeno de terbinafina:

cuadros negros: no hay condiciones de oclusión;

puntos negros: condiciones de oclusión.

25 Figura 3: patrón de difracción de polvo de rayos X con la

forma polimorfa A del malato de L-(-)-hidrógeno de terbinafina (Ejemplo 1 y 3).

Figura 4: patrón de difracción de polvo de rayos X con la forma polimorfa B del malato de L-(-)-hidrógeno de terbinafina (Ejemplo 2).

Figura 5: patrón de difracción de polvo de rayos X con malato de D-(+)-hidrógeno de terbinafina (Ejemplo 4).

Figura 6: patrón de difracción de polvo de rayos X con malato de DL-(+)-hidrógeno de terbinafina (Ejemplo 5).

En las Figuras 3 a 6: cps = intensidad de la señal (conteos por segundo); Deg. = ángulo de difracción (grados).

Los siguientes ejemplos ilustran la invención. Todas las temperaturas están en grados Celsius. P.f. = punto de fusión.

Ejemplo 1: Malato de L-(-)-hidrógeno de terbinafina (forma polimorfa A)

Se disuelven 15.54 gramos (53.32 milimoles) de base de terbinafina, y 6.79 gramos (50.65 milimoles) de ácido L-(-)-málico en 125 mililitros de acetato de etilo a 60°C. La solución se enfría a 0°C, y tiene lugar una cristalización lenta. Después de 2 días de reposar a 4°C, sólo se han precipitado unos cuantos cristales. Luego la mezcla se agita a 0°C. Después de 8 horas de agitación, la suspensión espesa

se diluye con 50 mililitros de acetato de etilo. La mezcla se filtra. La filtración es muy lenta. La torta se lava con 60 mililitros de acetato de etilo a 0°C, y se seca a 50°C/10 mbar durante 20 horas. Se obtiene el compuesto del título en la forma A (polvo blanco fino; p.f. aproximadamente 96°C; solubilidad a 25°C: en etanol, etano/agua, 2:8 por volumen/volumen, y acetato de etilo >30 miligramos/mililitro; en agua aproximadamente 12 miligramos/mililitro):

Análisis elemental:

10 Calculado: 70.57% C; 7.34% H; 3.29% N; 18.80% O.

Encontrado: 70.35% C; 7.39% H; 3.13% N; 18.94% O.

Patrón de difracción de polvo de rayos X: ver la Figura 3.

Ejemplo 2: Malato de L-(-)-hidrógeno de terbinafina

15 **(forma poliforma B)**

Se disuelven 200.0 gramos de base de terbinafina (686.2 milimoles) y 92.02 gramos de ácido L-(-)-málico en 1,500 mililitros de acetato de etilo a 60°C. Luego se permite que la solución transparente se enfríe lentamente. Se agregan 20 29.2 gramos de cristales de siembra de la forma B de malato de L-(-)-hidrógeno de terbinafina (obtenidos como se describe más adelante en la presente) a 32°C, y la suspensión se agita a temperatura ambiente (20-25°C) durante 20 horas. Luego la mezcla se enfría a 3°C durante 2 horas, y se agita durante 4 25 horas a esa temperatura. El precipitado resultante se filtra.

Los cristales se secan a 50°C, y a 10 mbar durante 20 horas. Se obtiene el compuesto del título en la forma B (polvo blanco; p.f. aproximadamente 96°C; solubilidad a 25°C en agua: 15 miligramos/mililitro; $[\alpha]^{20}$ a 365 nanómetros = 7.2° en metanol) (como un control del valor de rotación positivo, se disuelven 100 miligramos de la sal obtenida en 2 mililitros de cloruro de metileno, se agregan 3 mililitros de NaOH 0.2N, y se mide el valor de rotación de la fase acuosa que contiene el ácido L-(-)-málico libre: α^{20} = 0.134° a 546 nanómetros):

Análisis elemental:

Calculado: 70.57% C; 7.34% H; 3.29% N; 18.80% O.

Encontrado: 70.54% C; 7.37% H; 3.26% N; 18.75% O.

Patrón de difracción de polvo de rayos X: ver la Figura 4.

Se obtienen cristales de siembra de la forma B como sigue:

Se disuelven 19.57 gramos de base de terbinafina, y 8.55 gramos de ácido L-(-)-málico en 160 mililitros de acetato de etilo a 50°C, luego la solución se enfría a 25°C durante un periodo de 1 hora, y se siembra con 5 miligramos de cristales de malato de L-(-)-hidrógeno de terbinafina (forma A) obtenidos como se describe en el Ejemplo 1; la mezcla resultante se deja reposar sin agitar durante la noche por 18 horas, luego se agita lentamente a temperatura ambiente; la mezcla gelatinosa resultante se calienta a 50°C, y luego la

solución transparente resultante se enfría a 25°C y se inocula de nuevo, con 10 miligramos de cristales de la forma A de malato de L-(-)-hidrógeno de terbinafina; la mezcla se deja reposar durante 3 días a temperatura ambiente sin
5 agitación. Luego la mezcla resultante se agita suavemente de nuevo, y se establece lentamente la cristalización. Después de 24 horas de agitación adicional a temperatura ambiente, la mezcla se agita durante 3 horas a 3°C, se filtra y se seca. Se obtiene la forma B de malato de L-(-)-hidrógeno de
10 terbinafina cristalina.

Ejemplo 3: Malato de L-(-)-hidrógeno de terbinafina
(forma polimorfa A)

Se disuelven 400.0 gramos de base de terbinafina
15 (1.3725 moles) y 180.34 gramos de ácido L-(-)-málico (1.3450 moles) en 3,200 mililitros de isopropanol a 35°C. La solución se enfría a 25°C durante 45 minutos, y se siembra con 5.72 gramos de la forma A de malato de L-(-)-hidrógeno de terbinafina (obtenida como se describe en el Ejemplo 1).
20 Después de 27 horas de agitación a temperatura ambiente, la suspensión espesa se filtra. La filtración es lenta. Los cristales se lavan con 500 mililitros de isopropanol, y se secan a 50°C/15 mbar durante 24 horas. Se obtiene el compuesto del título en la forma A (polvo blanco fino; p.f.
25 aproximadamente, 96°C; solubilidad a 25°C: en etanol >50

72
71

miligramos/mililitro, acetato de etilo >30
miligramos/mililitro; en agua aproximadamente 12
miligramos/mililitro):

Análisis elemental:

5 Calculado: 70.57% C; 7.34% H; 3.29% N; 18.80% O.

Encontrado: 70.47% C; 7.12% H; 3.40% N; 18.60% O.

Patrón de difracción de polvo de rayos X: ver la Figura 3.

Ejemplo 4: Malato de D-(+)-hidrógeno de terbinafina

10 Se disuelven 8.70 gramos (29.8 milimoles) de base
de terbinafina, y 4.00 gramos (29.8 milimoles) de ácido D-
(+)-málico en 100 mililitros de acetato de etilo a 50°C. La
solución transparente se deja enfriar lentamente, y se
agregan 254 miligramos de cristales de siembra de malato de
15 D-(+)-hidrógeno de terbinafina (obtenidos como se describe
más adelante en la presente) a 25°C. Tiene lugar una
cristalización lenta, y la mezcla se agita a temperatura
ambiente (20-25°C) durante 63 horas. La suspensión espesa se
filtra. La filtración es muy lenta. La torta del filtro se
20 lava con 20 mililitros de acetato de etilo, y se seca a
50°C/10 mbar durante 20 horas. Se obtiene el compuesto del
título (p.f. aproximadamente 96°C; solubilidad en agua a
25°C: aproximadamente 7 miligramos/mililitro,
supersaturación; $[\alpha]^{20}$ a 365 nanómetros = -7.0° en metanol)
25 (como un control del valor de rotación negativo, se disuelven

100 miligramos de la sal obtenida en 2 mililitros de cloruro de metileno, se agregan 3 mililitros de NaOH 0.2N, y se mide el valor de rotación de la fase acuosa que contiene el ácido D-(+)-málico libre: $\alpha^{20} = +0.137^\circ$ a 546 nanómetros):

5 **Análisis elemental:**

Calculado: 70.57% C; 7.34% H; 3.29% N; 18.80% O.

Encontrado: 70.42% C; 7.45% H; 3.20% N; 18.92% O.

Patrón de difracción de polvo de rayos X: ver la Figura 5.

Los cristales de siembra se preparan como sigue:

10 Se disuelven 4.35 gramos de base de terbinafina y 2.00 gramos de ácido D-(+)-málico en 35 mililitros de isopropanol a 80°C. La solución se enfría a 25°C durante un período de 30 minutos, y se siembra con 20 miligramos de DL-(+)-malato de terbinafina (obtenido como se describe en el

15 Ejemplo 5). Entonces tiene lugar un proceso de cristalización muy lento. Después de 2 días de agitación a temperatura ambiente, sólo se ha precipitado una pequeña cantidad de cristales. La suspensión se filtra, y la torta se lava con 5 mililitros de isopropanol. Los cristales se secan a 50°C/10

20 mbar durante 20 horas. Se obtiene el malato de D-(+)-hidrógeno de terbinafina cristalino.

Ejemplo 5: Malato de DL-(+)-hidrógeno de terbinafina

Una suspensión de 8.70 gramos de base de

25 terbinafina (29.8 milimoles) y 4.00 gramos de ácido DL-málico

(29.8 milimoles) en aproximadamente 70 mililitros de isopropanol, se calienta a 80°C, y se obtiene una solución transparente. La solución se deja enfriar lentamente. Se agregan 10 gramos de malato de L-(-)-hidrógeno de terbinafina
5 (forma poliforma A, obtenida como se describe en el Ejemplo 1) a 25°C. La mezcla se agita durante 7 horas a temperatura ambiente. El precipitado resultante se filtra, y la torta del filtro se lava con 30 mililitros de isopropanol. Los cristales se secan a 50°C/10 mbar durante 20 horas. Se
10 obtiene el compuesto del título (polvo blanco; p.f. aproximadamente 107°C; solubilidad a 25°C: en etanol >50 miligramos/mililitro; en acetato de etilo aproximadamente 17 miligramos/mililitro; en agua aproximadamente 7 miligramos/mililitro):

15 **Análisis elemental:**

Calculado: 70.57% C; 7.34% H; 3.29% N; 18.80% O.

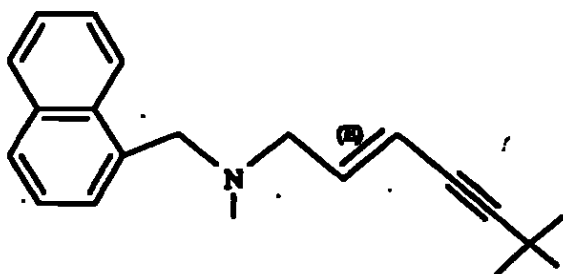
Encontrado: 70.49% C; 7.36% H; 3.16% N; 18.82% O.

Patrón de difracción de polvo de rayos X: ver la Figura 6.

REIVINDICACIONES

1. Una sal del compuesto de la fórmula I:

5



I

10 con ácido málico.

2. Un compuesto de acuerdo con la reivindicación 1, en la forma del malato de L-(-)-hidrógeno.

3. Un proceso para la preparación de un compuesto
15 de acuerdo con la reivindicación 1, el cual comprende hacer reaccionar el compuesto de la fórmula I en forma de base libre, con una forma de ácido málico apropiada, y recuperar de la mezcla de reacción la sal resultante.

4. Una composición farmacéutica que comprende un
20 compuesto de acuerdo con la reivindicación 1, junto con cuando menos un vehículo o diluyente farmacéuticamente aceptable.

5. Una composición farmacéutica que comprende al
compuesto de la fórmula I en forma de base libre o en forma
25 de sal farmacéuticamente aceptable diferente de una forma de

sal de adición de ácido málico, siempre que se prepare a partir de un compuesto de acuerdo con la reivindicación 1.

6. Un compuesto de acuerdo con la reivindicación 1, para utilizarse como un producto farmacéutico.

5 7. Un compuesto de acuerdo con la reivindicación 1, para utilizarse en la preparación de un medicamento.

8. El compuesto de la fórmula I, en forma de base libre o en forma de sal diferente de una forma de sal de adición de ácido málico, siempre que se prepare a partir de
10 un compuesto de acuerdo con la reivindicación 1.

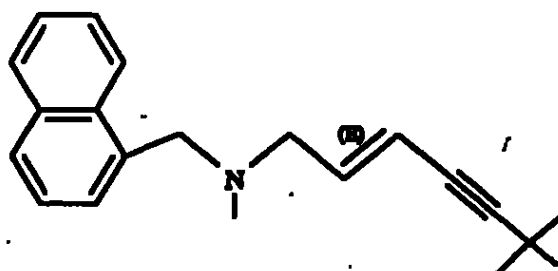
9. El uso de un compuesto de acuerdo con la reivindicación 1, en la preparación de un medicamento para el tratamiento de enfermedades susceptibles a terapia con el compuesto de la fórmula I en forma de base libre o en forma
15 de sal.

10. Un método para el tratamiento profiláctico o curativo de enfermedades fúngicas, tales como infección de senusitis fúngica u onicomycosis, el cual comprende la administración de una cantidad terapéuticamente efectiva de
20 un compuesto de acuerdo con la reivindicación 1 a un sujeto que necesite dicho tratamiento.

RESUMEN

La invención se refiere a sales del compuesto de la fórmula I:

5



I

10 con ácido málico,

a su preparación, a composiciones farmacéuticas correspondientes, y a su uso como antimicóticos.

* * * * *

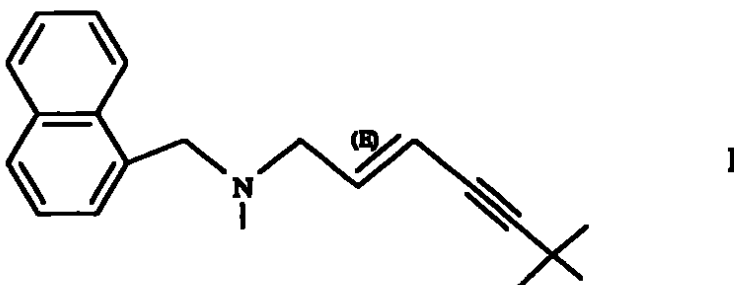
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20

MALIC ACID ADDITION SALTS OF TERBINAFINE**—ORGANIC COMPOUNDS—**

The invention relates to acid addition salts of allylamine antimycotics.

It concerns salts of the compound of formula I



with malic acid,

i.e. (E)-N-methyl-6,6-dimethyl-N-(1-naphthylmethyl)hept-2-en-4-yn-1-amine

in malic acid addition salt form,

hereinafter briefly named "the compounds of the invention".

The compounds of the invention are novel and improved pharmaceutical salts of the known compound of formula I.

A compound of the invention is in racemic or enantiomeric form. It is in malate or hydrogen malate, preferably in hydrogen malate, acid addition salt form. The malic acid moiety preferably is in racemic DL-(±)- or L-(-)-enantiomeric, especially in L-(-)-enantiomeric form. Particularly preferred are thus the DL-(±)- and the L-(-)-, especially the L-(-)-hydrogen malate.

The compounds of the invention exhibit polymorphism. The invention includes the compounds of the invention in any polymorphic form, e.g. form A or form B of the L-(-)-hydrogen malate as described hereunder.

The invention also includes a process for the preparation of a compound of the invention which comprises reacting the compound of formula I in free base form with an appropriate malic acid form and recovering from the reaction mixture the resultant salt.

The process of the invention may be effected in conventional manner, e.g. by reaction in an appropriate inert solvent such as isopropanol, acetic acid ethyl ester, isopropyl acetate, cyclopentanone, n-butanol or ethyl formate.

The compound of formula I in hydrochloric acid addition salt form and its use as an antimycotics e.g. in the treatment of mycosis caused by dermatophyte infection, is known i.a. from EP 24687 and its equivalents. It is available in free base or hydrochloric acid addition salt form under the trademark Lamisil[®], with the generic name terbinafine. Two further salt forms have also been mentioned in the literature, e.g. in EP 515310A1, the lactate and the ascorbate, in relation with pharmaceutical compositions for topical application on skin.

Terbinafine is an orally and topically effective anti-fungal agent. It is effective in a wide range of fungal diseases, including i.a. fungal sinusitis infection and onychomycosis. It is particularly useful against dermatophytes, contagious fungi that invade dead tissues of the skin or its appendages such as stratum corneum, nails, and hair. Such a nail fungus makes its home in the nail bed, shielded by the hard outer nail. Thus once infection is established under the nail, the nail itself provides the fungus with a protected environment that allows it to grow. The effects of these fungi on the nails may be unsightly, they seriously complicate foot-care, have a deleterious impact on the patient's overall quality of life and well-being and impair the patient's ability to work. If left untreated, the fungi can deform toenails permanently and lead to pain on walking. Additionally the fungi can lead to fissures in the skin encouraging bacterial infections. Serious complications as a result of these infections may occur in people suffering from diabetes such as diabetic foot syndrome including primary disease-related complications, e.g. gangrene that, ultimately, can be life-threatening or require amputation. Other high-risk patient sub-groups include patients infected with human immunodeficiency virus (HIV), patients with acquired immunodeficiency syndrome (AIDS), and patients with other types of immunosuppression (e.g. transplant recipients and patients on long term corticosteroid therapy). There is an increased prevalence of onychomycosis in the elderly (up to 30% by age 60). Microsporum, Trichophyton such as Trichophyton rubrum or Trichophyton mentagrophytes, and Epidermophyton such as Epidermophyton floccosum are those fungi commonly involved. Across medical disciplines, onychomycosis is well recognized as being arduous both to diagnose and to manage, particularly in the aged.

Terbinafine is also useful to treat toenail and fingernail onychomycosis (e.g. *Tinea unguium*) due to dermatophytes. Indeed terbinafine has opened up treatment for *Tinea unguium* caused by *Trichophyton*. For example it has been stated that treatment of toenails should be discouraged with the previously used standard, griseofulvin, because 1 to 2 years treatment is required, recurrence is usual and complete cure unlikely.

For the oral use in onychomycosis, terbinafine hydrochloride is normally administered as an immediate release tablet form containing 250 mg terbinafine once daily. Such a tablet, sold under the trademark Lamisil[®] releases terbinafine to the extent of 80 % over a 30 minute period as measured by standard in vitro dissolution studies, e.g. at pH 3 using the paddle method. Terbinafine treatment over 12 weeks is required. The progress of its clinical effectiveness is seen with growth of the healthy nail, pushing out and replacing the diseased unsightly nail containing debris and dead fungus. About 10 months is needed for a totally new toenail to form.

Although terbinafine is generally regarded to be as safe as any prescription drug, adverse events associated with its use have been reported. There have been a number of adverse events recorded, e.g. headaches, gastrointestinal symptoms (including diarrhea, dyspepsia, abdominal pain, nausea and flatulence), liver test abnormalities, e.g. enzyme abnormalities, dermatological symptoms such as pruritis, urticaria and rashes, and taste disturbances, e.g. loss of taste. These adverse events are in general mild and transient. Further adverse events include symptomatic idiosyncratic hepatobiliary dysfunction (e.g. cholestatic hepatitis), severe skin reactions such as Stevens-Johnson syndrome, neutropenia, and thrombocytopenia. Yet further adverse events may include visual disturbances such as changes in the ocular lens and retina, as well as allergic reactions including anaphylaxis, fatigue, vomiting, arthralgia, myalgia and hair loss. Terbinafine is a potent inhibitor of CYP2D6 and may cause clinically significant interactions when co-administered with substrates of this isoform, such as nortriptyline, desipramine, perphenazine, metoprolol, encainide and propafenone. Hereinafter any and all these events are referred to briefly as Adverse Events.

Pharmacokinetic and biopharmaceutical properties of terbinafine hydrochloride are known. Thus it is well absorbed. Peak drug plasma concentrations (hereinafter C_{max}) of about 1.3 $\mu\text{g/ml}$ (with about a 20 % variation, e.g. 0.9 to 1.6 $\mu\text{g/ml}$) appear in human subjects within 1 to 2 hours after administration of a single 250 mg terbinafine dose. The area under the curve over 24 hours (hereinafter AUC) is about 4.76 $\mu\text{g}\cdot\text{hour/ml}$. The increase in AUC is 42 % when terbinafine is administered with a fat-rich meal. In patients with renal impairment (e.g. creatinine clearance $\geq 50 \text{ ml/min}$) or hepatic cirrhosis, the clearance of terbinafine is reduced by approximately 50 %. In the steady state, e.g. when the trough and peaks are constant after several days dosing, in comparison to the single dose, C_{max} is 25 % higher and the AUC increases by a factor of 2.5. This is consistent with an effective half-life for terbinafine of about 36 hours.

Pharmacokinetic and absorption properties have been disclosed e.g. in J. Faergemann et al., Acta Derm. Venereol. (Stockh.) 77 (1997) 74-76. The site of absorption of terbinafine is, however, not known and there is no clinically proven correlation of effect with pharmacokinetic profile, so there is no rational starting point for developing pharmaceutical forms containing terbinafine with improved therapeutic effects.

Despite the very major contribution which terbinafine has made, the reported occurrence of undesirable Adverse Events has been an impediment to its wider oral use or application. The particular difficulties encountered in relation to oral dosing with terbinafine hydrochloride have inevitably led to restrictions in the use of terbinafine therapy for the treatment of relatively less severe or endangering disease conditions, e.g. Tinea pedis.

It has now been found that, unexpectedly, salts of the compound of formula I with malic acid possess particularly beneficial pharmacokinetic properties, and have further been found to possess a unique combination of favourable formulation properties which make them particularly suitable for the preparation of pharmaceutical compositions of terbinafine adapted for systemic and topical administration.

Thus the variability of pharmacokinetic parameters is considerably less when a malate salt of the compound of formula I is employed systemically than with known salts or the free base, e.g. the hydrochloride.

This appears i.a. from a pharmacokinetic study in animals involving 7 Beagle dogs weighing about 10 kg, aged about 5 years, upon oral administration of capsules prepared by mixing active terbinafine salt substance [hydrochloride or L-(-)-hydrogen malate; 62.5 mg base equivalent per capsule] with lactose in a ratio of 1:1 w/w and filling into appropriate hard gelatine capsules (particle size distribution similar for both salts).

The inter-animal variability in plasma exposure of terbinafine (as expressed by the coefficient of variation [hereinafter CV] of the area-under-the-curve [AUC] has been found to be distinctly reduced when the L-(-)-hydrogen malate salt of terbinafine is administered, namely 30 %, as compared with 39 % with the hydrochloride. The mean AUC values obtained thereby were, respectively, 392 and 348 ng.hour/ml, showing even a slight increase in absolute plasma exposure with the hydrogen malate salt.

The mean C_{max} values obtained thereby are 134 and 146 ng/ml for the L-(-)-hydrogen malate and the hydrochloride, respectively, with corresponding CV values 26 % and 47 %, respectively, a further indication of reduced variability of pharmacokinetic parameters when a malate salt is used.

It can be expected therefrom that in human subjects, a similarly reduced variability of pharmacokinetic parameters is obtained, and thus even more stable efficacy of treatment with terbinafine in antimycotic indications may be envisaged, even at very high dosages, in particular upon oral administration, e.g. in the oral treatment of onychomycosis.

Further, the compounds of the invention may also be employed topically, e.g. on the nail, as appears for example from the following in vitro penetration/permeation assay:

Human cadaveric toe nails are used in a Franz cell (Figure 1) modified to accept cadaveric human toenails by having a pair of flexible rings made of a silicone elastomer (PDMS) having good sealant properties to adequately mount hard nails, using liquid scintillation counting (LSC) (picogram limit of detection) to measure the increase in radioactivity in the acceptor compartment. Each measurement is effected in triplicate. 90 randomly selected nails are exposed for 72 hours to a solution of 100 μ l of 14 C-labelled terbinafine hydrochloride or terbinafine L-(-)-hydrogen malate (form A) solution [25 μ Bq/ml; 1 active product; 5 % 1,2-propylene glycol; 2 % Cetomacrogol-1000^R (polyoxyethylene-glycol-1000-monoacetyether); 25 ethanol 94 ; 67 distilled water] (w/w). Each area of

the nail exposed to the formulation has a 9 mm diameter (about 64 mm²). Exposure is effected under occlusive (chamber closed to air) and non-occlusive (chamber open to air) conditions.

The radiolabelled product is detectable in the buffer-filled receptor chamber from about 8 hours of incubation. Its concentration in the receptor chamber as measured by LSC increases with incubation time and concentration of applied formulation. A total of 24 penetration chambers are used in parallel. Each formulation is measured in triplicate.

The result is as appears from Figure 2: under both occlusive (black dots) and non-occlusive (black squares) conditions, at 72 hours substantial permeation is observed (about 63 ng and 41 ng, respectively).

Further, it has been found that the compounds of the invention surprisingly possess favourable formulation properties. They thus form crystals more readily than the hydrochloride or the free base. Further, the crystals of e.g. the L-(-)-hydrogen malate salt exhibit various polymorphic forms. Polymorphs have different dissolution rates, milling behaviour and stability, e.g. in galenical forms where the pharmaceutically active compound is in solid form, such as tablets or suspensions, and they influence bioavailability. The surprising presence of polymorphism is therefore advantageous in terms of improved processability, such as with polymorph particularly stable thermodynamically, in formulations with compound in solid form, e.g. tablets or suspensions, or with polymorph having a particularly high dissolution rate or solubility, in formulations with dissolved compound, e.g. nail lacquers. The compounds of the invention are therefore better processable for e.g. large scale tablet formulation; they also have favourable penetration/permeation properties and can thus readily be formulated into topical forms, such as nail lacquers. Additionally, they possess good solubility in water and many organic solvents, a prerequisite for good bioavailability: thus at 25°C, the L-(-)-hydrogen malate is soluble up to about 12-15 mg/ml in water and > 30 mg/ml in ethyl acetate, as compared with 6.7 mg/ml in water and 0.7 mg/ml in ethyl acetate for the hydrochloride. Further, they are non-hygroscopic, thus providing stable formulations while minimizing the risk of intrinsic chemical breakdown.

They therefore show a unique combination of good processability, good solubility and non-hygroscopicity which makes them remarkably suitable for the preparation of pharmaceutical compositions of terbinafine.

The invention further includes:

- a pharmaceutical composition comprising a compound of the invention together with at least one pharmaceutically acceptable carrier or diluent;
- a pharmaceutical composition comprising the compound of formula I in free form or pharmaceutically acceptable salt form other than a malic acid addition salt form, whenever prepared from a compound of the invention;
- a compound of the invention for use as a pharmaceutical;
- a compound of the invention for use in the preparation of a medicament;
- a compound of the invention whenever prepared by a process as defined above;
- a compound of formula I in free base form or salt form other than a malic acid addition salt form, whenever prepared from a compound of the invention;
- the use of a compound of the invention in the preparation of a medicament for the treatment, e.g. orally, of diseases susceptible of therapy with the compound of formula I in free base form or salt form, such as fungal diseases;
- a process for the preparation of a pharmaceutical composition which comprises mixing a compound of the invention together with at least one pharmaceutically acceptable carrier or diluent; and
- a method for the prophylactic or curative treatment of fungal diseases such as fungal sinusitis infection or onychomycosis, comprising administration of a therapeutically effective amount of a compound of the invention to a subject in need of such treatment.

Pharmaceutical compositions incorporating a compound of the invention are preferably compounded in unit dosage form, e.g. by filling into capsule shells, e.g. soft or hard gelatine capsule shells, or by tableting or some other moulding process. Thus unit dosage forms suitable for administration once or twice daily, e.g. depending on the particular purpose of therapy, the phase of therapy, etc., will appropriately comprise half or the total daily dose contemplated. Such compositions may be administered twice or three times a week. Preferably the compositions are administered once-a-day.

The amount of compound of the invention will of course vary, e.g. depending on to what extent other components are present, the mode of administration and the treatment desired. In general, however, it will be present in an amount within the range of from about 0.1 % to about 35 % by weight based on the total weight of the composition. The total daily dosage of active compound (expressed in free base equivalent) is, for example, from about 50 mg to about 500 mg daily, e.g. 250 mg daily, or 400 mg, 600 mg or 700 mg daily, conveniently given, for example, in divided doses up to 4 times a day. Unit dosage forms comprise e.g. from about 12.5 mg to about 800 mg of compound of the invention (expressed in free base equivalent) in admixture with at least one solid or liquid pharmaceutically acceptable carrier or diluent.

The compounds of the invention may be administered in similar manner to known standards for use in such indications.

They may be admixed with conventional, chemotherapeutically acceptable carriers or diluents and optionally further excipients, and administered e.g. orally, e.g. in the form of formulations such as tablets and capsules. A preferred tablet formulation includes a compound of the invention, a compression aid such as microcrystalline cellulose, an additive to provide sheen to the tablet such as anhydrous dibasic calcium phosphate, a disintegrant such as sodium starch glycolate, and a lubricant such as magnesium stearate. A preferred capsule formulation includes a compound of the invention, an inert diluent, a dried disintegrant and a lubricant as described above.

Alternatively, they may be administered topically, e.g. in the form of formulations, e.g. lotions, solutions, ointments or creams, such as nail lacquers, or parenterally or intravenously. The concentration of active substance will of course vary, e.g. depending on the compound of the invention employed, the treatment desired and the nature of the form or formulation used. In general, satisfactory results are obtained in e.g. topical formulations at concentrations of from about 0.1 % to about 10 %, particularly from about 0.5 % to about 2 %, especially about 1 % by weight.

With the present invention there are thus also provided novel terbinafine compositions containing the compounds of the invention which meet or substantially reduce the difficulties in terbinafine therapy hitherto encountered. In particular they may contain

terbinafine in sufficiently high and constant concentrations to permit convenient oral once-a-day administration, while at the same time achieving improved safety and tolerability in terms of fewer Adverse Events.

Thus the present invention enables reduction of terbinafine treatment times required to achieve effective therapy, reducing the exposure time to terbinafine and improving the global safety profile. In addition it allows closer standardization as well as optimization of on-going daily dosage requirements for individual subjects receiving terbinafine therapy as well as for groups of patients undergoing equivalent therapy. By closer standardization of individual patient therapeutic regimens, dosaging parameters for particular patient groups as well as monitoring requirements may be reduced, thus substantially reducing the cost of therapy.

Further pharmacokinetic properties of pharmaceutical compositions containing the compounds of the invention may be determined in standard animal and human pharmacological (bioavailability) trials. For example one standard pharmacological trial may be carried out in healthy male or female non-smoking volunteers aged between 18 to 45 years having within 20 % of the ideal body weight. The trial may be a single-dose crossover application. The subjects are domiciled for 24 hours. Blood samples are taken for 1, 2, 4, 8, 16, 32 and 72 hours after administration of a pharmaceutical composition containing a compound of the invention and tested for terbinafine. Terbinafine blood or plasma concentrations may be determined in conventional manner, e.g. by HPLC/UV or LC-MS analytical techniques. Safety is judged according to a standard checklist based on Adverse Event symptoms after 1 week. Preferably the dose of terbinafine salt is 400, 600 or 700-800 mg of base equivalent per day. The safety of terbinafine at such a dose over the short duration of treatment is remarkable. The oral compositions of the invention preferably exhibit a C_{max} of 100-250 %, e.g. 100-150 %, of that shown by 250 mg immediate release terbinafine hydrochloride tablets, e.g. administered as a single dose and/or in the steady state, e.g. once a day for 7 days.

Pharmacokinetic drug skin and nail concentration studies may be carried out according to the same principles as set out for the above-mentioned standard pharmacological trials. For example a clinical trial may be effected with daily dosing of compositions containing a compound of the invention over a 3-week treatment period.

Tablets containing the compounds of the invention are useful for the same indications as for known immediate release terbinafine hydrochloride tablets. The utility of compounds of the invention may be observed in standard clinical tests or standard animal models. For example, one can ascertain dosages of compositions containing a compound of the invention giving AUC plasma levels of terbinafine equivalent to AUC plasma levels giving a therapeutic effect on administration of known terbinafine hydrochloride oral dosage forms, e.g. a tablet. Pharmaceutical compositions containing a compound of the invention are particularly and surprisingly well-tolerated with regard to the Adverse Events mentioned above, they provoke fewer Adverse Events when co-administered with CYP2D6 substrates such as nortriptyline, desipramine, perphenazine, metoprolol, encainide and propafenone.

A randomized double-blind positive-controlled and placebo-controlled study may e.g. be effected with subjects having onychomycosis of the toenail confirmed by microscopy and culture. Treatment is carried out over 12 weeks. Clinical trials may be effected in several hundred patients to ascertain the freedom from Adverse Events. However, therapeutic efficacy may already be shown in trials with 25 patients aged over 12 years. Safety is evaluated by an Adverse Event report of clinical aspects and vital signs. Efficacy is determined by microscopy, culture procedures and visually looking at signs and symptoms. Efficacy is seen in patients with the fungi described above, especially *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Epidermophyton floccosum*. Patients include those with predisposing factors such as impaired blood circulation, peripheral neuropathy, diabetes mellitus, damage from repeated minor trauma, and limited immune defects as well as AIDS. Patients have (i) distal lateral subungual onychomycosis, starting at the hyponychium spreading proximally to the nail bed and matrix, (ii) proximal subungual onychomycosis, wherein the fungus infects the cuticle and eponychium to reach the matrix where it becomes enclosed into the nail plate substance, (iii) total dystrophic onychomycosis, and (iv) superficial white onychomycosis. If desired plasma concentrations of terbinafine may be evaluated in conventional manner or as described herein. Concentrations of terbinafine in the nail may be evaluated from nail clipping followed by analysis.

Explanation of the Figures:

Figure 1: Schematic representation of a Franz cell.

Figure 2: Penetration/permeation assay: amount recovered in receptor chamber (in ng) vs. time (in hours) with 1 % terbinafine-(L)-(-)-hydrogen malate solution:
black squares: no occlusion conditions;
black dots: occlusion conditions.

Figure 3: X-ray powder diffraction pattern with terbinafine L-(-)-hydrogen malate polymorph form A (Examples 1 and 3).

Figure 4: X-ray powder diffraction pattern with terbinafine L-(-)-hydrogen malate polymorph form B (Example 2).

Figure 5: X-ray powder diffraction pattern with terbinafine D-(+)-hydrogen malate (Example 4).

Figure 6: X-ray powder diffraction pattern with terbinafine DL-(±)-hydrogen malate (Example 5).

In Figures 3 to 6: cps = signal intensity (counts per second); Deg. = angle of diffraction (degrees).

The following Examples illustrate the invention. All temperatures are in degrees Celsius. m.p. = melting point.

Example 1: Terbinafine L-(-)-hydrogen malate (polymorph form A)

15.54 g (53.32 mmol) terbinafine base and 6.79 g (50.65 mmol) L-(-)-malic acid are dissolved in 125 ml of ethyl acetate at 60°. The solution is cooled to 0° and slow crystallisation takes place. After 2 days standing at 4° only a few crystals have precipitated. The mixture is then stirred at 0°. After 8 hours stirring the thick suspension is diluted with 50 ml of ethyl acetate. The mixture is filtered. Filtration is very slow. The cake is washed with 60 ml of ethyl acetate at 0° and dried at 50° / 10 mbar for 20 hours. The title compound in form A is obtained (fine white powder; m.p. ~96°; solubility at 25°: in ethanol, ethane/water 2:8 v/v, and ethyl acetate > 30 mg/ml; in water ~12 mg/ml):

Elementary analysis:**Calc.:** 70.57 % C; 7.34 % H; 3.29 % N; 18.80 % O**Found:** 70.35 % C; 7.39 % H; 3.13 % N; 18.94 % O**X-ray powder diffraction pattern:** see Figure 3.**Example 2: Terbinafine L-(-)-hydrogen malate (polymorph form B)**

200.0 g terbinafine base (686.2 mmoles) and 92.02 g L-(-)-malic acid are dissolved in 1500 ml of ethyl acetate at 60°. The clear solution is then allowed to slowly cool down. 29.2 g terbinafine L-(-)-hydrogen malate form B seed crystals (obtained as described hereunder) is added at 32° and the suspension stirred at room temperature (20-25°) for 20 hours. The mixture is then cooled to 3° over 2 hours and stirred for 4 hours at that temperature. The resultant precipitate is filtered. The crystals are dried at 50° and 10 mbar for 20 hours. The title compound in form B is obtained (white powder; m.p.: ~96°; solubility at 25° in water: 15 mg/ml; $[\alpha]^{20}$ at 365 nm = +7.2° in methanol) (as a control of the positive rotation value, 100 mg salt obtained is dissolved in 2 ml of methylene chloride, 3 ml NaOH 0.2 N is added, and the rotation value of the aqueous phase containing free L-(-)-malic acid is measured: $\alpha^{20} = -0.134^\circ$ at 546 nm):

Elementary analysis:**Calc.:** 70.57 % C; 7.34 % H; 3.29 % N; 18.80 % O**Found:** 70.54 % C; 7.37 % H; 3.26 % N; 18.75 % O**X-ray powder diffraction pattern:** see Figure 4.

Seed crystals of form B are obtained as follows:

19.57 g terbinafine base and 8.55 g L-(-)-malic acid are dissolved in 160 ml of ethyl acetate at 50°, the solution is then cooled to 25° over a period of 1 hour, and seeded with 5 mg terbinafine L-(-)-hydrogen malate (form A) crystals obtained as described in Example 1; the resultant mixture is allowed to stay unstirred overnight for 18 hours, then slowly stirred at room temperature; the resultant gelatinous mixture is warmed to 50° and the resultant clear solution then cooled to 25° and inoculated again, with 10 mg terbinafine-L-(-)-hydrogen malate form A crystals; the mixture is allow to rest for 3 days at room temperature without stirring. The resultant mixture is then gently stirred again and crystallization slowly sets in. After 24 hours further stirring at room temperature, the mixture is stirred for 3 hours at 3°, filtered and dried. Crystalline terbinafine-L-(-)-hydrogen malate form B is obtained.

Example 3: Terbinafine L-(-)-hydrogen malate (polymorph form A)

400.0 g terbinafine base (1.3725 moles) and 180.34 g L-(-)-malic acid (1.3450 moles) are dissolved in 3200 ml of isopropanol at 35°. The solution is cooled to 25° over 45 minutes and seeded with 5.72 g terbinafine-L-(-)-hydrogen malate form A (obtained as described in Example 1). After 27 hours stirring at room temperature the thick suspension is filtered. Filtration is slow. The crystals are washed with 500 ml of isopropanol and dried at 50° / 15 mbar for 24 hours. The title compound in form A is obtained (fine white powder; m.p. ~96°; solubility at 25°: in ethanol >50 mg/ml, ethylacetate >30 mg/ml; in water ~12 mg/ml):

Elementary analysis:

Calc.: 70.57 % C; 7.34 % H; 3.29 % N; 18.80 % O

Found: 70.47 % C; 7.12 % H; 3.40 % N; 18.60 % O

X-ray powder diffraction pattern: see Figure 3.

Example 4: Terbinafine D-(+)-hydrogen malate

8.70 g (29.8 mmol) terbinafine base and 4.00 g (29.8 mmol) D-(+)-malic acid are dissolved in 100 ml of ethyl acetate at 50°. The clear solution is allowed to slowly cool down and 254 mg terbinafine-D-(+)-hydrogen malate seed crystals (obtained as described hereunder) is added at 25°. Slow crystallization takes place and the mixture is stirred at room temperature (20-25°) for 63 hours. The thick suspension is filtered. Filtration is very slow. The filter cake is washed with 20 ml of ethyl acetate and dried at 50° / 10 mbar for 20 hours. The title compound is obtained (m.p. ~96°; solubility in water at 25°: ~7 mg/ml, supersaturation; $[\alpha]^{20}_{365 \text{ nm}} = -7.0^\circ$ in methanol) (as a control of the negative rotation value, 100 mg salt obtained is dissolved in 2 ml of methylene chloride, 3 ml NaOH 0.2 N is added, and the rotation value of the aqueous phase containing free D-(+)-malic acid is measured: $\alpha^{20} = +0.137^\circ$ at 546 nm):

Elementary analysis:

Calc.: 70.57 % C; 7.34 % H; 3.29 % N; 18.80 % O

Found: 70.42 % C; 7.45 % H; 3.20 % N; 18.92 % O

X-ray powder diffraction pattern: see Figure 5.

Seed crystals are prepared as follows:

4.35 g terbinafine base and 2.00 g D(+)-malic acid are dissolved in 35 ml of isopropanol at 80°. The solution is cooled to 25° over a period of 30 minutes, and seeded with 20 mg terbinafine-DL-(±)-malate (obtained as described in Example 5). A very slow crystallization process takes then place. After two days stirring at room temperature only a small amount of crystals has precipitated. The suspension is filtered and the cake is washed with 5 ml of isopropanol. The crystals are dried at 50° / 10 mbar for 20 hours. Crystalline terbinafine-D-(+)-hydrogen malate is obtained.

Example 5: Terbinafine DL-(±)-hydrogen malate

A suspension of 8.70 g terbinafine base (29.8 mmol) and 4.00 g DL-malic acid (29.8 mmol) in about 70 ml of isopropanol is heated to 80° and a clear solution is obtained. The solution is allowed to slowly cool down. 10 mg terbinafine-L-(-)-hydrogen malate (polymorph form A, obtained as described in Example 1) are added at 25°. The mixture is stirred for 7 hours at room temperature. The resultant precipitate is filtered and the filter cake is washed with 30 ml of isopropanol. The crystals are dried at 50° / 10 mbar for 20 hours. The title compound is obtained (white powder; m.p. ~107°; solubility at 25°: in ethanol >50 mg/ml; in ethyl acetate ~17 mg/ml; in water ~7 mg/ml):

Elementary analysis:

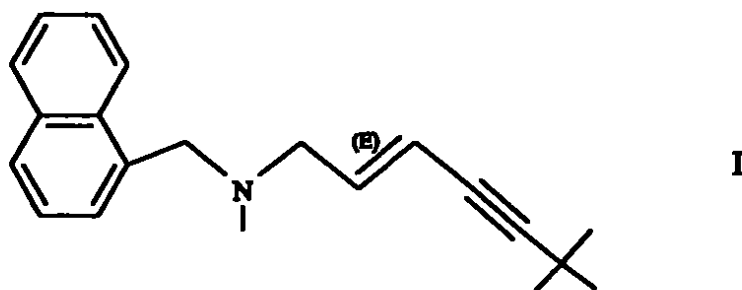
Calc.: 70.57 % C; 7.34 % H; 3.29 % N; 18.80 % O

Found: 70.49 % C; 7.36 % H; 3.16 % N; 18.82 % O

X-ray powder diffraction pattern: see Figure 6.

Claims:

1. A salt of the compound of formula I

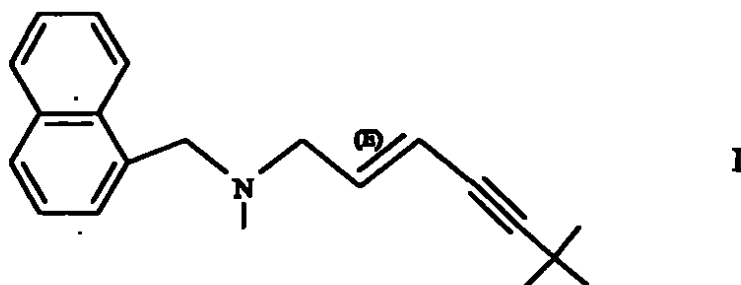


with malic acid.

2. A compound according to claim 1 in the form of the L-(-)-hydrogen malate.
3. A process for the preparation of a compound according to claim 1 which comprises reacting the compound of formula I in free base form with an appropriate malic acid form and recovering from the reaction mixture the resultant salt.
4. A pharmaceutical composition comprising a compound according to claim 1 together with at least one pharmaceutically acceptable carrier or diluent.
5. A pharmaceutical composition comprising the compound of formula I in free base form or pharmaceutically acceptable salt form other than a malic acid addition salt form, whenever prepared from a compound according to claim 1.
6. A compound according to claim 1 for use as a pharmaceutical.
7. A compound according to claim 1 for use in the preparation of a medicament.
8. The compound of formula I in free base form or a salt form other than a malic acid addition salt form, whenever prepared from a compound according to claim 1.
9. The use of a compound according to claim 1 in the preparation of a medicament for the treatment of diseases susceptible of therapy with the compound of formula I in free base form or salt form.
10. A method for the prophylactic or curative treatment of fungal diseases such as fungal sinusitis infection or onychomycosis, comprising administration of a therapeutically effective amount of a compound according to claim 1 to a subject in need of such treatment.

Abstract:**ORGANIC COMPOUNDS**

The invention concerns salts of the compound of formula I



with malic acid,

their preparation, corresponding pharmaceutical compositions and their use as antimycotics.

Figure 1

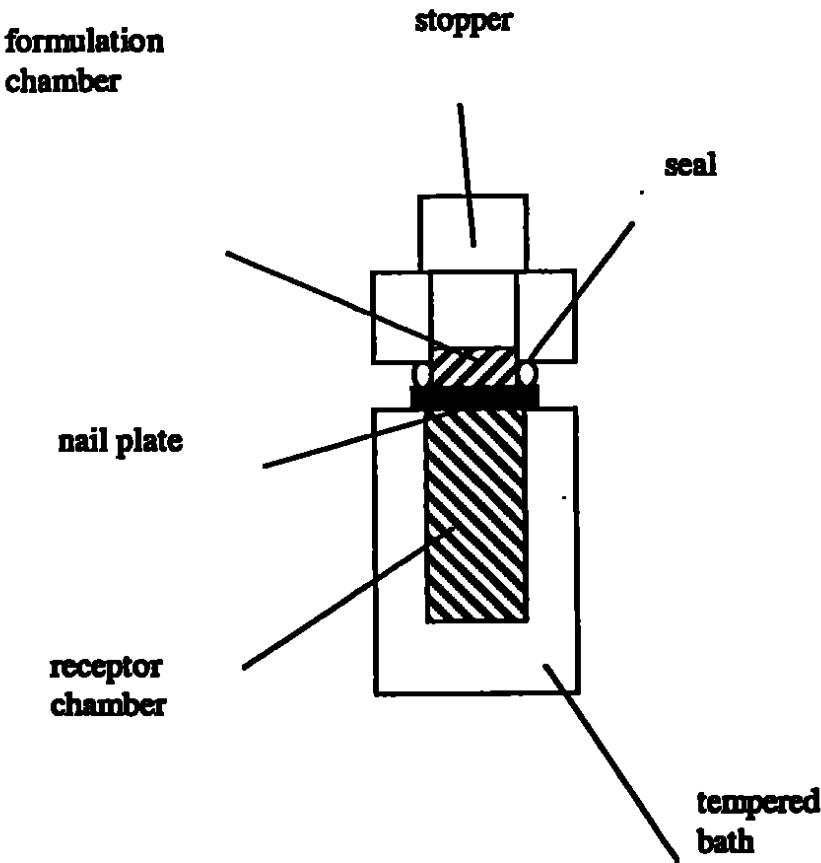
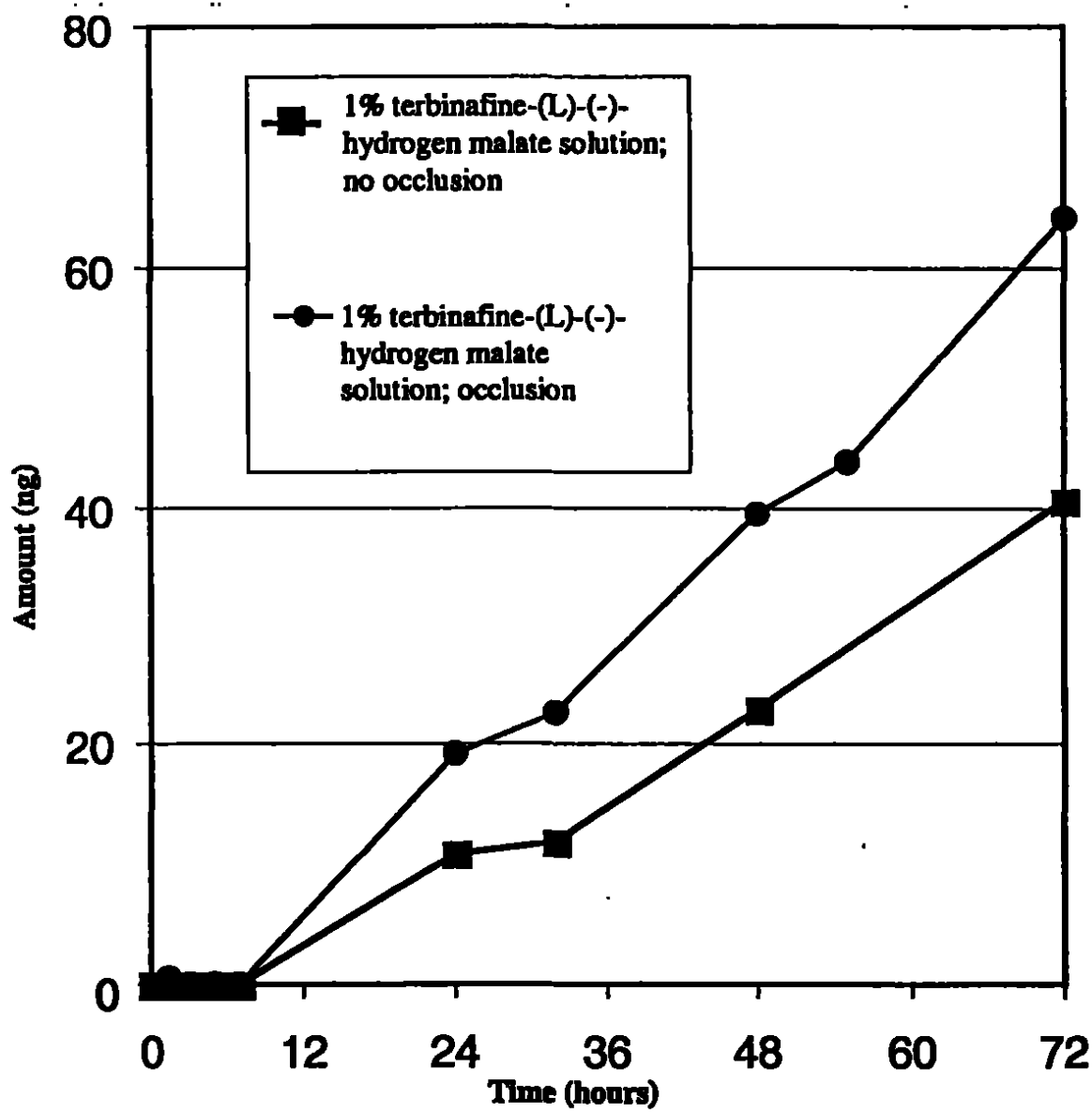
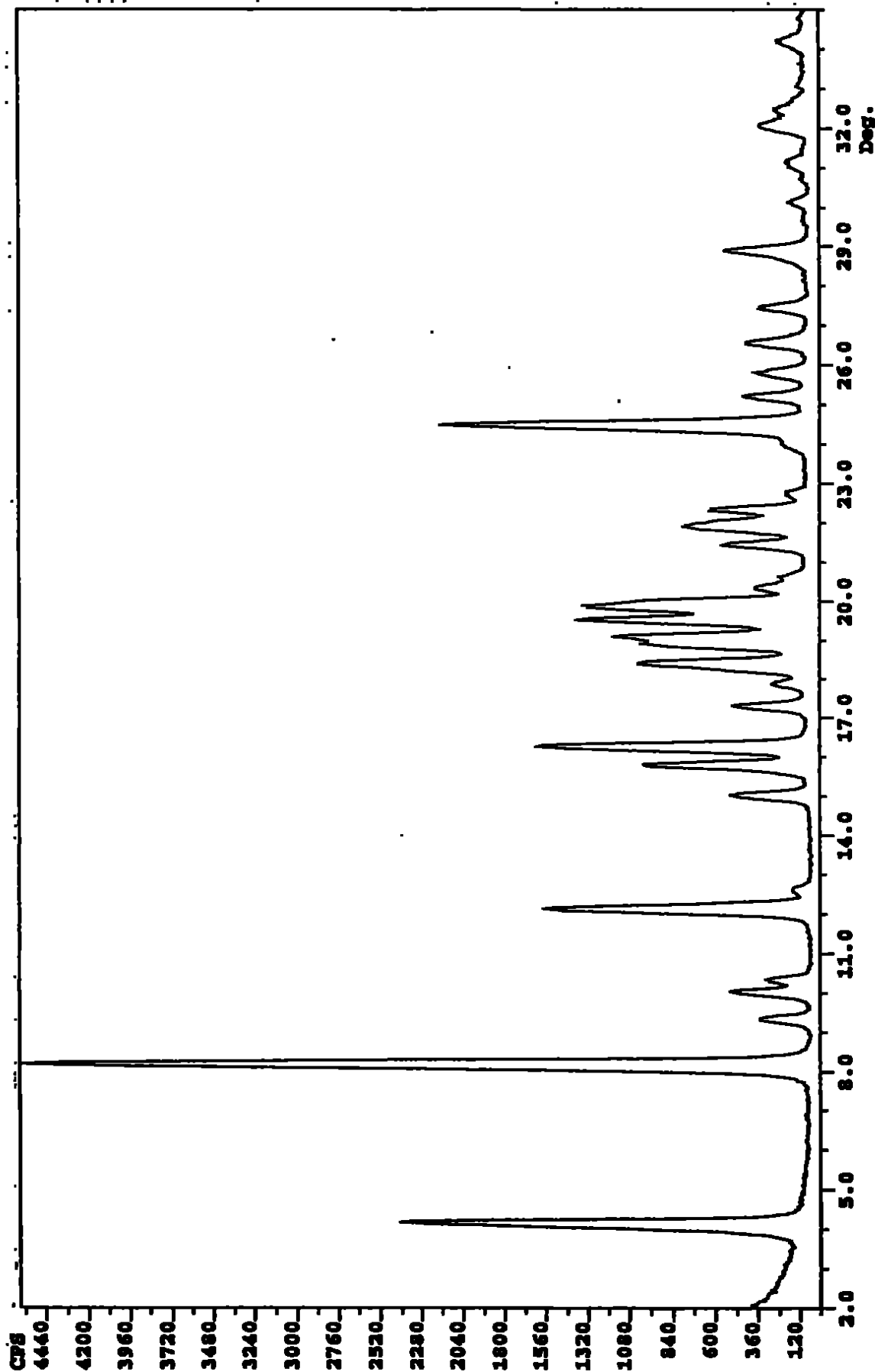


Figure 2



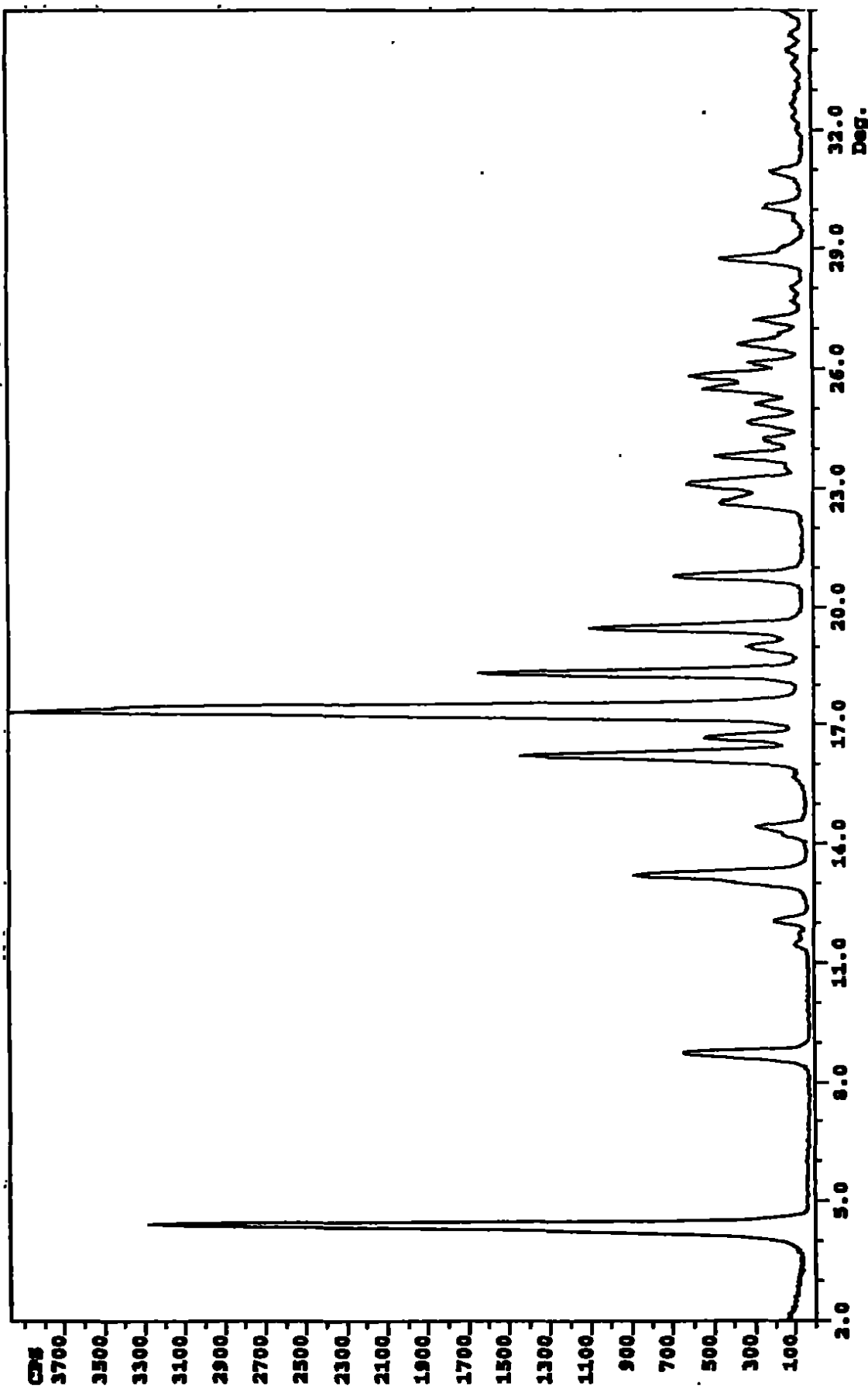
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95

Figure 3



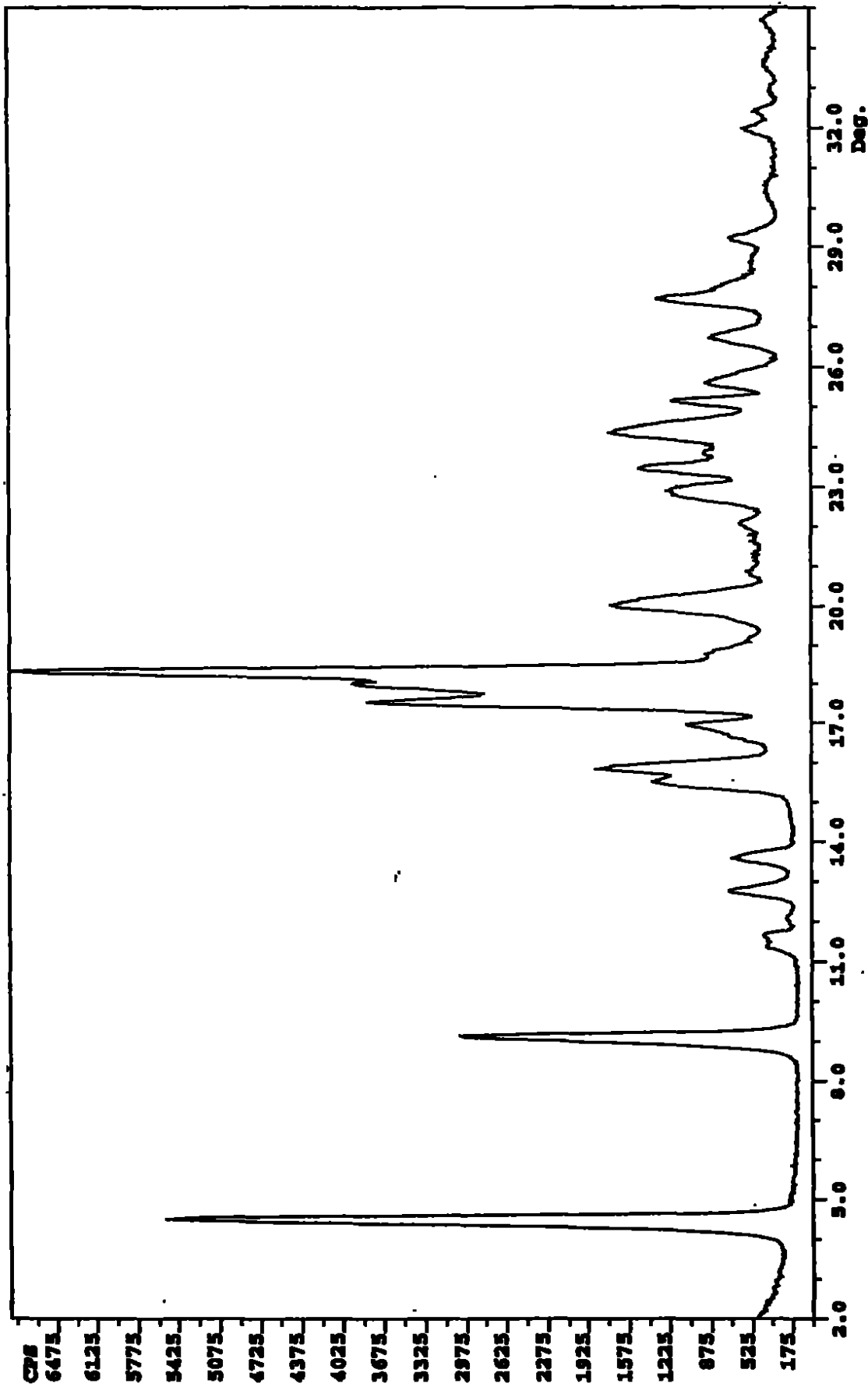
416 97
96

Figure 4



98
5/6 97

Figure 5



98

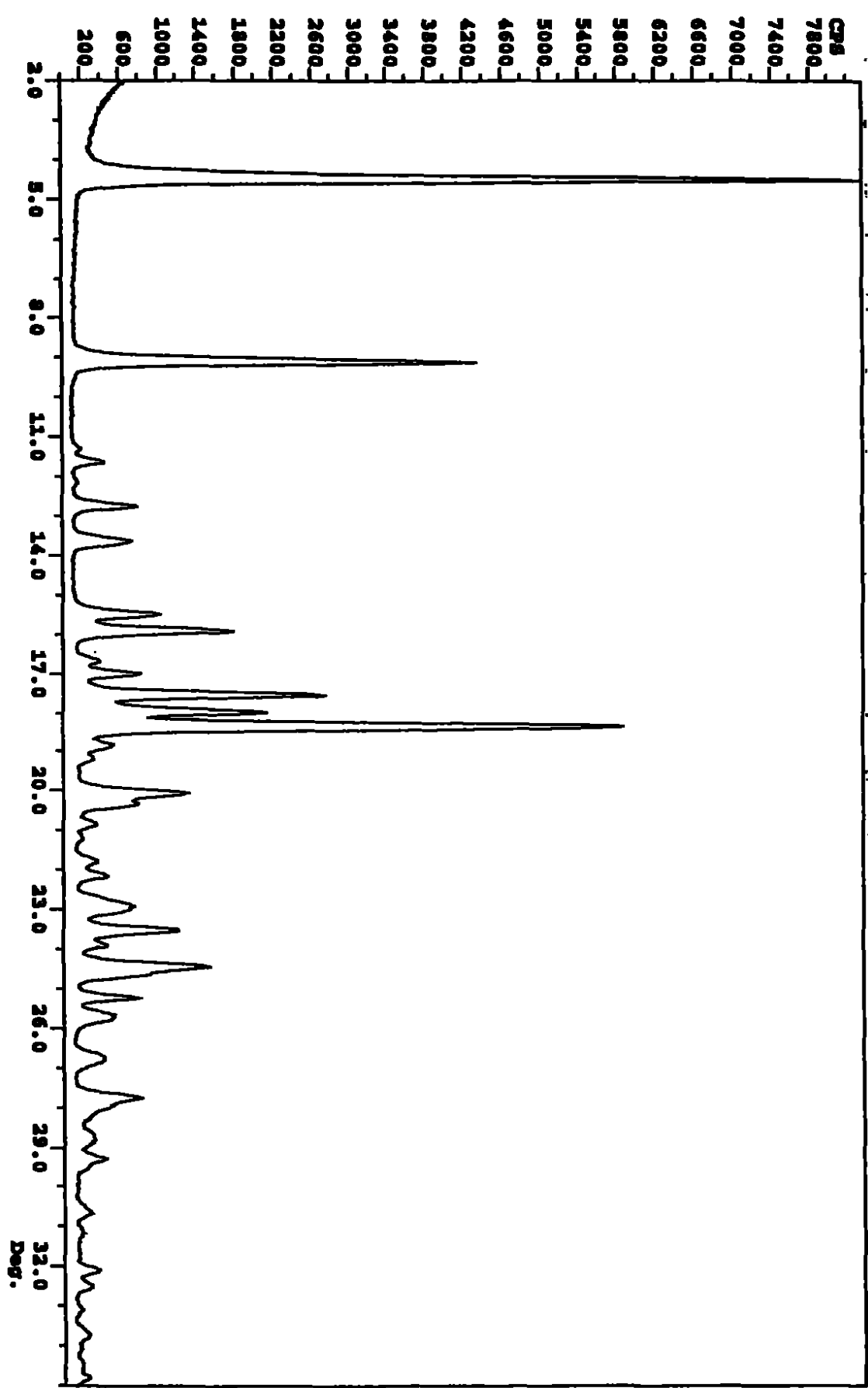


Figure 6

4-31862

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
- Indicación de que se solicita la concesión de una patente.	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes.	()	()
- Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable:



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