



**Industria y Comercio**

S U P E R I N T E N D E N C I A

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

**PATENTE DE INVENCION**

21. EXPEDIENTE No.

05-96127

54. TÍTULO

NUEVO COMPUESTO INTERMEDIO PARA LA PREPARACION DE  
IMIDAZOPIRIDINAS TERAPEUTICAMENTE ACTIVAS.

51. CLASIFICACIÓN INTERNACIONAL

COTE 47/00  
A61K31/4178

71. SOLICITANTE

ALTAVA PHARMA AG.

DOMICILIO

KONSTANZ, ALEMANIA

74. APODERADO

JIMENA ESCOBAR URIBE

22. BOGOTÁ, D. C.,

SEPTIEMBRE 22, 2005

SS

**FORMULARIO ÚNICO DE SOLICITUD DE PATENTE  
PCT**

**ENTRADA EN FASE NACIONAL**

14-12-05

**SOLICITUD DE:**



Patente de Invención



Patente de Modelo de Utilidad



Capítulo I.



Capítulo II.

2

**SOLICITANTE  
(71)**

Nombre: **ALTANA PHARMA AG.**  
Dirección: Byk-Gulden-Strasse 2, 78467  
Konstanz, Alemania.  
Nacionalidad o Domicilio: Konstanz,  
Alemania  
Lugar de Constitución : Alemania  
Teléfono: Fax:  
E-mail

**IDENTIFICACIÓN**

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Número

3

**REPRESENTANTE  
O APODERADO  
(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 39.779.452 T.P.68.228

4

**INVENTOR (ES)  
(72)**

Nombre: **VER ANEXO**  
Dirección:  
Nacionalidad o domicilio:

folio 9

5

**PCT (86)**

Solicitud Internacional No. PCT/EP2004/050780 Fecha 13 de mayo de 2004  
Publicación Internacional No. WO 2004/101566 A1 Fecha 25 de noviembre de 2004

6 **TÍTULO (54)**

**NUEVO COMPUESTO INTERMEDIO PARA LA PREPARACIÓN DE  
IMIDAZOPIRIDINAS TERAPÉUTICAMENTE ACTIVAS.**

7 **Clasificación Internacional (51)**

C07D 471/14

A61K31/4178.

8 **Prioridad**

(33) País de Origen  
Oficina de Patentes Europea

(32) Fecha  
14 de mayo de 2003

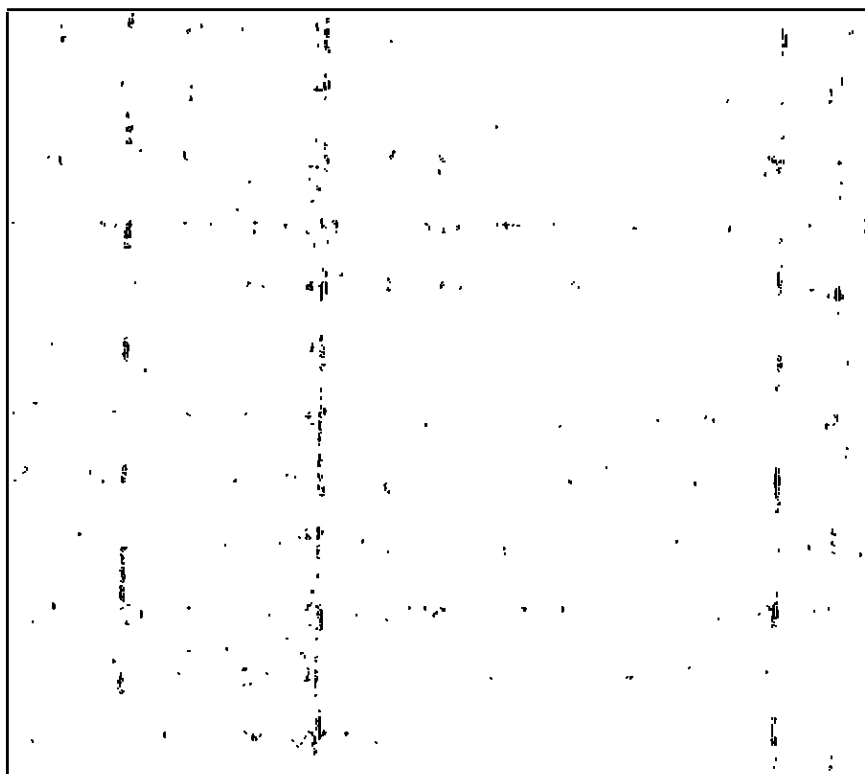
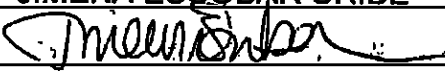
(31) Número de Solicitud  
03010785.8

SI ☒ NO ☐

9 **Comprobante de pago No.** 05 - 72.103

**Fecha** 16 de septiembre de 2005

- ☐ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- ☐ Poderes si fuere el caso
- ☐ 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 \* Opinión escrita.

**11 FIGURA CARACTERÍSTICA****12 Solicito la concesión de la patente**NOMBRE: JIMENA ESCOBAR URIBEFIRMA: 

C.C. 39.779.452 de Usaquén T.P. 68.228

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. \_\_\_\_\_

9882

SUPERINTENDENCIA Y COMERCIO  
Adicacion : 05096127 00000000 Folios: 50  
Fecha (AMD): 2005-09-22 15:44:51  
Tramite : 011 PCI-PAJEN: 379 FASE NAL: 411 PRESENTAL  
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 72,103  
FECHA : SEPTIEMBRE 16 DE 2005

## \*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE             | TIPO PAGO    | BANCO         | CUENTA      | No. PAGO | FECHA PGO  | Vr. PAGO     |
|-------------------------|--------------|---------------|-------------|----------|------------|--------------|
| ESCOBAR URIBE ASOCIADOS | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 42211058 | 16/09/2005 | 4,204,000.00 |

## \*\*\*\*\* CONCEPTO \*\*\*\*\*

| CANT. | RENTISTICO              | CONCEPTO                            | TOTAL CONCEPTO |
|-------|-------------------------|-------------------------------------|----------------|
| 1     | 50005-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE IN | 443,000.00     |
|       |                         | TOTAL :                             | \$ 443,000.00  |

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS



2342  
3

## POWER OF ATTORNEY DOCUMENTO DE PODER

The undersigned

acting on behalf of and representing  
**ALTANA PHARMA AG**  
domiciled at  
**KONSTANZ, ALEMANIA**  
hereby appoints  
**JIMENA ESCOBAR-URIBE and/or IGNACIO ESCOBAR-URIBE**  
domiciled at Bogota, Colombia  
**CARRERA 11 A No. 94-76 OF. 305-306**

as our true and legal attorneys with the necessary powers: 1. to apply to the administrative, judicial and police authorities of the Republic of Colombia, in any instance or appeal, for obtaining registration of patents, utility models, industrial designs, commercial ensigns and names, trademarks, domain names, copyrights and neighbouring rights, plant varieties, health licenses as well as their assignments, extensions, renewals, changes of name and domicile; 2. to prepare, apply for, obtain, execute and register contracts, licenses, authorizations and registrations of any kind; 3. to intervene as plaintiffs or defendants, in any instance or appeal, before any judge, court, tribunal, corporation, public officer or authority in any judicial, administrative or police action, such as: actions dealing with commercial ensigns and names; oppositions against trademark registrations; caducity and nullity actions; recovery actions, actions arising from obtainment and working of license agreements; actions dealing with unfair competition; criminal actions; actions claiming indemnity for damages, complaints or remarks on all sort of industrial property matters; the performance of precautionary measures, and in any other similar action, measure or appeal related to industrial property matters, copyrights and neighbouring rights and obtentor of plant varieties rights. To this effect, we hereby authorize them to file applications, make descriptions, amendments, protests, declarations, oppositions, cancellations, appeals and claims; to pay taxes, quotas and liens as provided by law; to waive or abandon granted rights or rights in process of being granted, to receive all kind of documents and securities; to issue the respective releases and, in general to take, before said authorities, pertinent steps to the above-mentioned purposes and take all measures they may deem advisable to protect our interests, with all other necessary legal faculties, and we hereby declare as good and valid whatever the attorneys should do to our benefit.

This power comprises the authority to ratify or confirm on our behalf any action, as well as the faculty of receiving, desisting, transacting, compromising, conciliating, substituting and revoking substitutions, taking notifications and appointing judicial or extra-judicial attorneys.

Signed at **10. 2002**  
on **20. 78. 62 Konstanz**

Dr. U. Sprger

ppä. A. Mächler

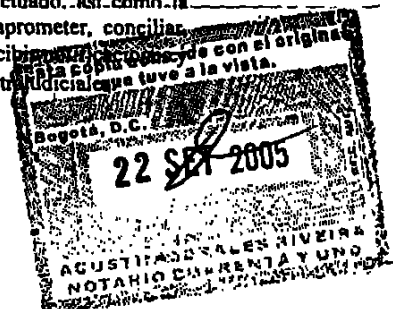
El suscrito

obrando en nombre y representación de  
**ALTANA PHARMA AG**  
con domicilio en  
**KONSTANZ, ALEMANIA**  
 nombra a  
**JIMENA ESCOBAR-URIBE y/o IGNACIO ESCOBAR-URIBE**  
domiciliados en Bogotá, Colombia  
**CARRERA 11 A No. 94-76 OF. 305-306**

apoderados verdaderos y legales con poder especial, amplio y suficiente: 1. para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía en cualquier instancia o recurso, la obtención de patentes de invención, modelos de utilidad, diseños industriales, registro de marcas, nombres de dominio, registro de derechos de autor y derechos conexos, registro de variedades vegetales, depósito de nombres comerciales y enseññas, registros sanitarios, así como sus traspasos, prórrogas, renovaciones, cambios de nombre y de domicilio; 2. elaborar, tramitar, solicitar, obtener, realizar, ejecutar y registrar contratos, licencias, autorizaciones y registros de cualesquiera clase; 3. intervenir como demandante o como demandado en cualquier instancia y recurso, y ante cualquier juez, entidad, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía, tales como acciones derivadas del nombre o enseña comerciales; observaciones u oposición al registro de marcas; acciones de caducidad y nulidad; acciones reivindicatorias; acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales y civiles; acciones de indemnización de perjuicios, reclamos u observaciones a cualquier asunto, sobre propiedad industrial; el ejercicio de medidas cautelares y cualesquiera otras acciones, medidas o recursos similares relacionados con la propiedad industrial, los derechos de autor y derechos conexos y los derechos de obtentor de variedades vegetales. A este efecto, los facultamos para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de nuestros intereses, con todas las demás facultades necesarias y por este documento desde ahora declaramos válido y bueno todo cuanto los apoderados hicieren en nuestro beneficio.

Este poder comprende la facultad de ratificar o confirmar en nuestro nombre lo actuado, así como la facultad de desistir, transigir, comprometer, conciliar, sustituir y revocar sustituciones, recibir notificaciones, nombrar apoderados judiciales o extra-judiciales o extinguirlos.

Firmado en  
el



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**Notariat I Konstanz**  
**I UR 1222 /2002**

This is to certify that before me, Volker Tamm, Notary Public in and for Konstanz, Germany, duly admitted and sworn in, there appeared this day

1. Dr. Ulrich Sorger, board of director,
2. Alexander Mächler, officer with statutory authority,

personally known to me, the Notary,

address: Byk-Gulden-Str. 2, D-78467 Konstanz,

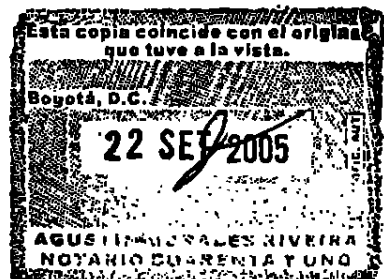
acting in their capacities of board of director and officer with statutory authority respectively of the public limited company named ALTANA Pharma AG, Konstanz, and as such authorized to represent said company jointly with full legal effect, identified in their said capacities by my examination of the commercial register files of the District-Court of Konstanz - file number: HR B 1925 -, and acknowledged their foregoing signatures as their free act and deed.

Witness my hand and seal.

Tamm, Notary public  
Notariat I Konstanz



D-78462 Konstanz, 21 oktober 2002



**Notariat Konstanz**  
**I UR 1222 /2002**

## **Unterschriftsbeglaubigung**

Vorstehende Unterschriften für die Firma ALTANA Pharma AG mit dem Sitz in Konstanz wurden heute eigenhändig vor mir vollzogen von den persönlich bekannten Herren:

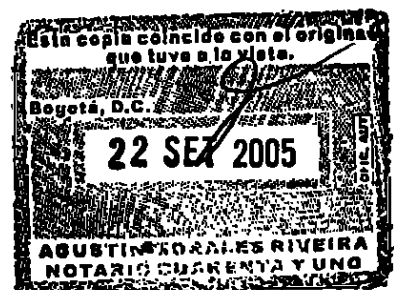
1. Dr. Ulrich Sorger, Vorstandsmitglied,
2. Alexander Mächler, Prokurist

beide geschäftsansässig Byk-Gulden-Strasse 2, 78467 Konstanz, und werden als echt öffentlich beglaubigt.

Aufgrund heutiger Einsicht in das Handelsregister beim Amtsgericht Konstanz HR B 1925 bescheinige ich als Notar, dass die Firma ALTANA Pharma AG mit dem Sitz in Konstanz im Handelsregister beim Amtsgericht Konstanz unter HR B 1925 eingetragen ist und dass Herr Dr. Ulrich Sorger als Vorstand und Herr Alexander Mächler als Prokurist zur gemeinsamen Vertretung dieser Firma befugt sind.

78462 Konstanz, den 21.10.2002  
Notariat I Konstanz

Tamir  
Notar



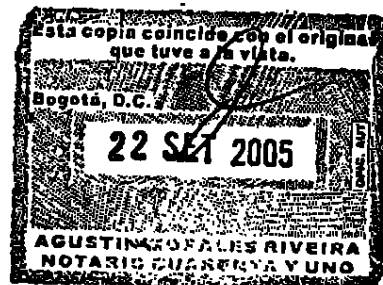
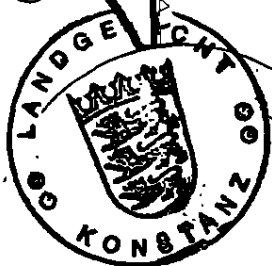
## Apostille

(Convention de La Haye du 5 octobre 1961)

1. Land: Bundesrepublik Deutschland  
Diese öffentliche Urkunde
2. ist unterschrieben von  
**Notariatsdirektor Tamm**
3. in seiner Eigenschaft als  
Notar
4. sie ist versehen mit dem Dienstsiegel  
des Notariats Konstanz

### Bestätigt

5. in Konstanz
6. am 24.10.2002
7. durch Vorsitzenden Richter am Landgericht Basel  
beim Landgericht Konstanz
8. unter Nr. E 910 a (AR 483/02)
9. Siegel/Stempel
10. Unterschrift



2

Traducción Oficial del Alemán de la Autenticación de Firmas y la Apostilla adjuntas al poder que la compañía ALTANA Pharma AG domiciliada en Konstanz, Alemania, otorga a Jimena Escobar-Uribe y/o Ignacio Escobar-Uribe

---

Notariado de Konstanz

I Registro Notarial 1222/2002

Autenticación de Firmas

Se autentican oficialmente las firmas que aparecen anteriormente, que fueron ejecutadas el día de hoy en mi presencia en nombre de la compañía ALTANA Pharma AG por los Señores:

1. Dr. Ulrich Sorger, Presidente de la Junta Directiva,
2. Alexander Mächler, Apoderado,

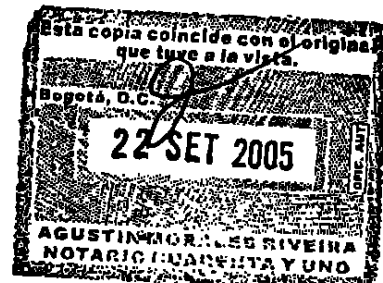
quienes son conocidos personalmente por el suscrito Notario y quienes tienen ambos su domicilio comercial en Byk-Gulden-Strasse 2, 78467 Konstanz.

Al mismo tiempo, luego la revisión llevada a cabo el día de hoy en el Registro Comercial HRB 1925 del Juzgado Municipal de Konstanz, certifico en mi calidad de Notario que la compañía ALTANA Pharma AG domiciliada en Konstanz está registrada ante el Juzgado Municipal de Konstanz bajo el número HRB 1925, y que el Señor Dr. Ulrich Sorger en su calidad de Presidente de la Junta Directiva y el Señor Alexander Mächler en su calidad de Apoderado se encuentran autorizados para representar conjuntamente a la mencionada compañía.

78467 Konstanz, 21.10.2002

Notariado I de Konstanz

Tamm, Notario en Konstanz (Firma y Sello Oficial)



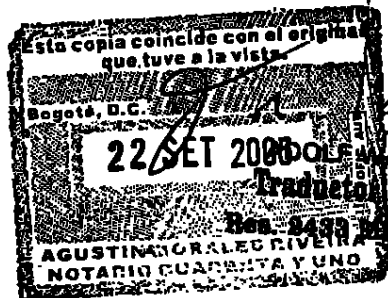
**APOSTILLA**

(Convención de La Haya del 5 de Octubre de 1961)

1. País: República Federal de Alemania  
Este documento público
2. Ha sido firmado por: El Director de Notariado Tamm
3. Actuando en calidad de: Notario Público
4. Y lleva el sello oficial: Del Notariado de Konstanz

**Confirmado**

5. En: Konstanz
6. El día: 24.10.2002
7. Por: El Juez Presidente en el Tribunal Regional  
de Basilea en el Tribunal Regional de Konstanz
8. Bajo el No.: E 910 a (AR 483/02)
9. Sello: TRIBUNAL REGIONAL DE KONSTANZ
10. Firma: (firma ilegible)



MINISTERIO DE RELACIONES  
EXTERIORES

*Morales Riveira*

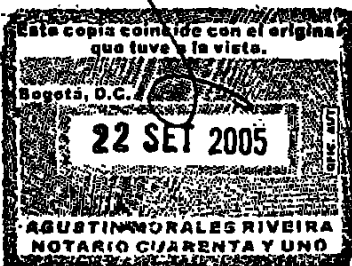
028257

COTA FINA APARECE EN EL  
DOCUMENTO DESEMPENA  
LAS FUNCIONES INDICADAS

NO SE ASUME  
RESPONSABILIDAD DEL TEXTO

2002 NOV 19 12 45

JEFE DE LEGALIZACIONES  
SANTAFE DE BOGOTA D.C.



## ANEXOS

### INVENTORES

1.)

**MUELLER, Bernd**

( Buecklestr. 84a, 78467 Konstanz, Alemania );

2.)

**ZIMMERMANN, Peter**

( Radolfzeller Str. 71a, 78467 Konstanz, Alemania );

3.)

**SCHEUFLE, Christian**

( Lindenstr. 28, 78234 Engen-Neuhausen, Alemania );

4.)

**KOHL, Bernhard**

( Zum Bruehl 9, 78465 Konstanz, Alemania ).

Solicito expresamente a nombre de ALTANA PHARMA AG., sociedad constituida de conformidad con las leyes de Alemania, domiciliada en Byk-Gulden-Strasse 2, 78467 Konstanz, Alemania, el otorgamiento de Patente para la invención titulada "NUEVO COMPUESTO INTERMEDIO PARA LA PREPARACIÓN DE IMIDAZOPIRIDINAS TERAPÉUTICAMENTE ACTIVAS".

Clase: C07D 471/14



**JIMENA ESCOBAR URIBE**

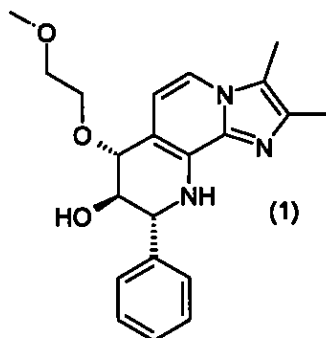
**C.C. 39.779.452 de Usaquen.**

**T.P. 68.228**

Extracto de pb. 6ho M

**RESUMEN**

El invento se refiere a la sal por adición de ácido  
1,5-naftaleno disulfónico del compuesto de la fórmula  
5 la 1.



El compuesto de acuerdo con el invento es un valioso  
10 compuesto intermediado para la preparación de compues-  
tos terapéuticamente activos.

**Nuevo compuesto intermedio para la preparación de  
imidazopiridinas terapéuticamente activas**

**Campo técnico**

5

El invento se refiere a nuevos compuestos que se usan en la industria farmacéutica como valiosos compuestos intermedios para la preparación de compuestos activos.

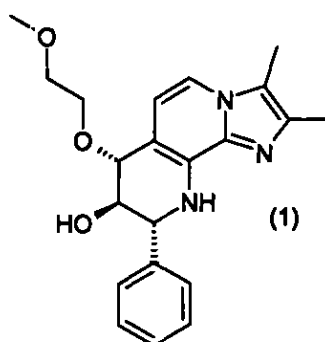
10 **Técnica anterior**

Las solicitudes de patentes internacionales WO 98/42707, WO 00/17200, WO 00/26217, WO 00/63211, WO 01/72756, WO 01/72754, WO 01/72757, WO 02/34749, 15 WO 03/016310, WO 03/014120 y WO 03/014123 describen derivados tricíclicos de imidazopiridina, que tienen un modelo de sustitución muy específico, que deberían ser apropiados para el tratamiento de trastornos gástricos e intestinales, y a ciertos procedimientos para su 20 preparación.

**Descripción del Invento**

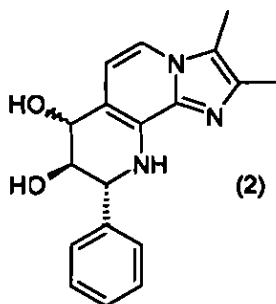
El invento se refiere a un nuevo procedimiento para la 25 producción de los derivados tricíclicos de imidazopiridina antes mencionados, y a valiosos compuestos intermedios usados en dichos procedimientos.

El invento se refiere por lo tanto, en un primer aspecto, a la sal por adición de ácido 1,5-naftaleno 30 disulfónico del compuesto de la fórmula 1



Resulta conocido para una persona experta en la especialidad el hecho de que el compuesto de acuerdo con el invento, si es que es aislado, por ejemplo, en forma cristalina, puede contener diversas cantidades de disolventes. El invento, por lo tanto, comprende también todos los solvatos, y en particular todos los hidratos de la sal por adición de ácido 1,5-naftaleno disulfónico del compuesto de la fórmula 1.

La sal por adición de ácido 1,5-naftaleno disulfónico del compuesto de la fórmula 1 de acuerdo con el invento se puede preparar a partir de los compuestos de la fórmula 2

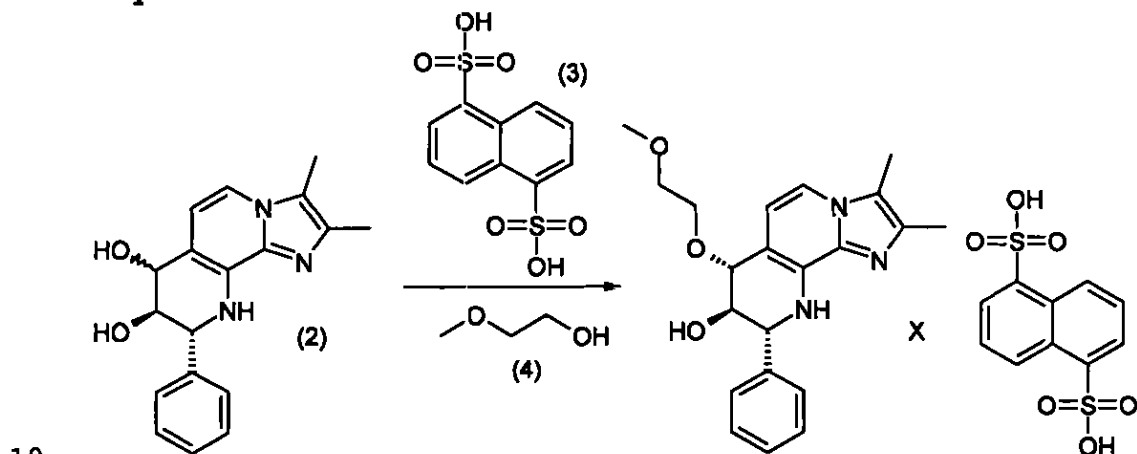


como se muestra en el esquema 1, por reacción con el ácido 1,5-naftaleno disulfónico de la fórmula 3 y con el 2-metoxi-etanol de la fórmula 4. La reacción de una mezcla de dioles cis/trans o del compuesto, ya sea cis o trans, del diol de la fórmula 2, conduce exclusivamente a la precipitación de la deseada sal por adición de ácido 1,5-naftaleno disulfónico del compuesto de la

fórmula 1. En condiciones ácidas de reacción, los centros quirales en la posición 7 del diol de la fórmula 2 y del compuesto de la fórmula 1 se epimerizan, y se establece un equilibrio entre los compuestos cis y trans.

- 5 La sal por adición de ácido 1,5-naftaleno disulfónico del compuesto de la fórmula 1 es el único compuesto que precipita a partir de estas mezclas de reacción.

**Esquema 1:**



- El ácido 1,5-naftaleno disulfónico y el compuesto de la fórmula 1 forman sales por adición de ácidos de acuerdo con el invento con diferentes relaciones molares del ácido 1,5-naftaleno disulfónico y del compuesto de la fórmula 1.
- 15

- Preferidas sales por adición de ácidos de acuerdo con el invento son aquellas en las que la relación molar entre el ácido 1,5-naftaleno disulfónico y el compuesto de la fórmula 1 está situada entre 1 : 1 y 2 : 1.
- 20

- Sales por adición de ácidos especialmente preferidas de acuerdo con el invento son aquellas en las que la relación molar entre el ácido 1,5-naftaleno disulfónico y el compuesto de la fórmula 1 está situada entre 1 : 1 y 1,2 : 1.
- 25

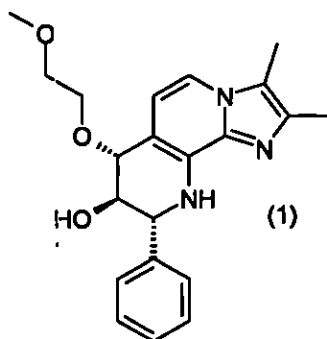
La reacción mostrada en el esquema 1 se lleva a cabo ya sea sin ningún disolvente o bien en un apropiado disolvente o en una apropiada mezcla de disolventes. La reacción se lleva a cabo preferiblemente en un apropiado disolvente.

La reacción se lleva a cabo preferiblemente en la ausencia de agua.

Preferidos disolventes para la reacción mostrada en el esquema 1 son cetonas tales como por ejemplo acetona, metil-etil-cetona o isobutil-metil-cetona o éteres tales como por ejemplo dietil-éter, diisopropil-éter o metil-terc.-butil-éter.

Un disolvente particularmente preferido para la reacción mostrada en el esquema 1 es isobutil-metil-cetona.

El invento se refiere además al uso de la sal por adición de ácido 1,5-naftaleno disulfónico del compuesto de la fórmula 1 para la preparación del compuesto de la fórmula 1



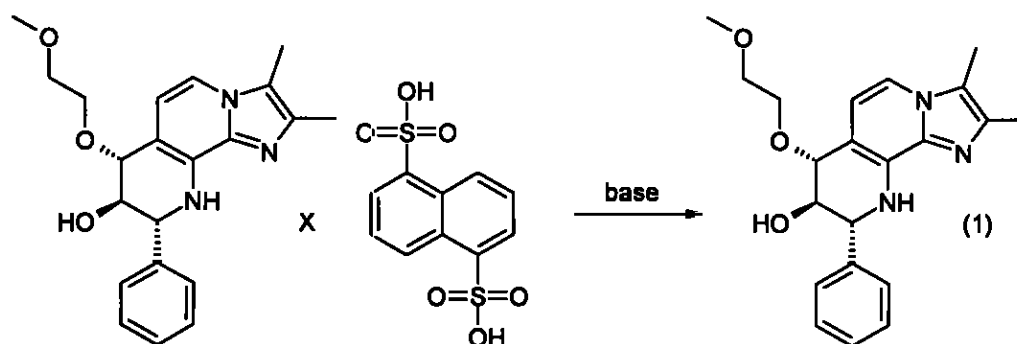
que es conocido a partir de la solicitud de patente internacional WO 00/17200, y sus sales.

Sales apropiadas de compuestos de la fórmula 1 a este respecto son especialmente todas las sales por adición de ácidos. Se puede hacer una mención particular de las sales farmacológicamente tolerables de los ácidos inor-

gánicos y orgánicos habitualmente usados en la tecnología farmacéutica. Las sales apropiadas son sales por adición de ácidos solubles en agua e insolubles en agua, con ácidos tales como, por ejemplo, ácido clorhídrico, ácido bromhídrico, ácido fosfórico, ácido nítrico, ácido sulfúrico, ácido acético, ácido cítrico, ácido D-glucónico, ácido benzoico, ácido 2-(4-hidroxibenzoí1)benzoico, ácido butírico, ácido sulfosalicílico, ácido maleico, ácido láurico, ácido málico, ácido fumárico, ácido succínico, ácido oxálico, ácido tartárico, ácido embónico, ácido esteárico, ácido toluenosulfónico, ácido metanosulfónico o ácido 3-hidroxí-2-naftoico, en que los ácidos se emplean en la preparación de sales - dependiendo de que esté implicado un ácido mono- o poli-básico, y dependiendo de cuál sea la sal que se desee - en una relación cuantitativa equimolar o en una relación diferente de ésta.

Estas sales del compuesto de la fórmula 1 se mencionan en la solicitud de patente WO 00/17200 y no son apropiadas para el procedimiento de acuerdo con el presente invento como se muestra en el esquema 1.

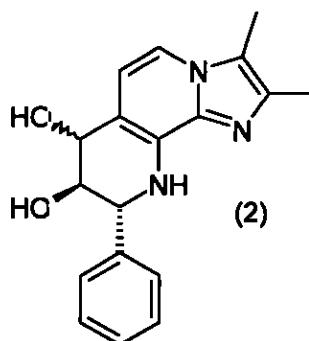
El procedimiento de uso de la sal por adición de ácido 1,5-naftaleno disulfónico del compuesto de la fórmula 1 de acuerdo con el invento para la preparación del compuesto de la fórmula 1 se lleva a cabo, como se muestra en el esquema 2, haciendo reaccionar la sal por adición de ácido 1,5-naftaleno disulfónico del compuesto de la fórmula 1 con una base, y luego realizando su tratamiento.

**Esquema 2:**

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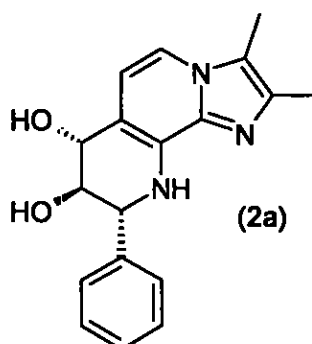
Los compuestos dioles de partida de la fórmula 2 para la preparación de la sal por adición de ácido 1,5-naftaleno disulfónico del compuesto de la fórmula 1 de acuerdo con el invento, son conocidos (véase el documento WO 00/17200).

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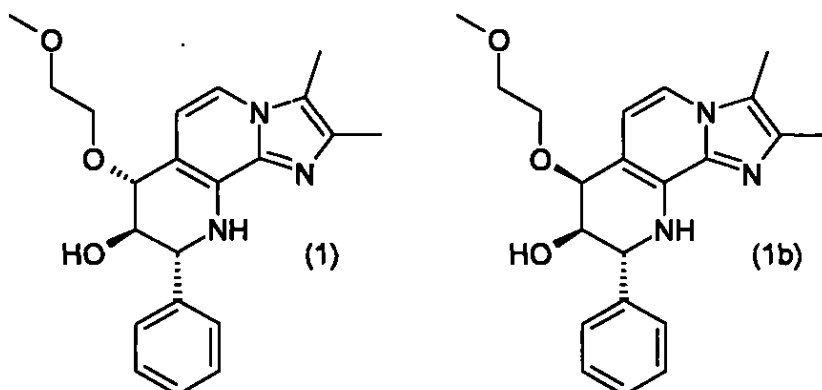


En la solicitud de patente WO 00/17200, el compuesto trans diol de la fórmula 2a

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se usa para la preparación del compuesto de la fórmula 1 por reacción del compuesto de la fórmula 2a con 2-metoxi-etanol y ácido sulfúrico. Esta reacción descrita en el documento WO 00/17200, que usa ácido sulfúrico, conduce a la formación del indeseado compuesto de la fórmula 1b en cantidades iguales o incluso mayores que las del deseado compuesto de la fórmula 1.



10

La desventaja de la formación del indeseado compuesto de la fórmula 1b en la reacción de eterificación de los compuestos de la fórmula 2 descritos en el documento WO 00/17200, se puede solventar con el presente invento. El uso del ácido 1,5-naftaleno disulfónico en vez del ácido sulfúrico en la reacción de compuestos de la fórmula 2 con 2-metoxi-etanol conduce, con un alto rendimiento, a la exclusiva formación de la sal por adición de ácido 1,5-naftaleno disulfónico del compuesto de la fórmula 1, que se puede convertir, en una subsiguiente etapa, en el compuesto de la fórmula 1.

Los siguientes ejemplos sirven para ilustrar el invento de manera adicional, sin restringirlo. Las abreviaturas representan: min a minuto(s), h a hora(s) y p.f. a punto de fusión.

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**Ejemplos**

**Sal con ácido 1,5-naftaleno disulfónico de**  
**[(7R,8R,9R)-2,3-dimetil-8-hidroxi-7-(2-metoxi-etoxi)-**  
 5 **9-fenil-7,8,9,10-tetrahidro-imidazo-[1,2-h][1,7]-**  
**naftiridina]**

Se disolvieron 18,8 g (52,2 mmol) de ácido 1,5-naftaleno disulfónico tetrahidrato en 100 ml de 2-metoxi-etanol. 70 ml del 2-metoxi-etanol se separaron  
 10 por destilación en vacío (50 mbar) para eliminar el agua de cristalización. Se añadió una solución de 5,00 g (16,2 mmol) de una mezcla de (7R,8R,9R)-7,8-dihidroxi-2,3-dimetil-9-fenil-7,8,9,10-tetrahidro-  
 15 imidazo[1,2-h][1,7]-naftiridina y (7S,8R,9R)-7,8-dihidroxi-2,3-dimetil-9-fenil-7,8,9,10-tetrahidro-imidazo[1,2-h][1,7]-naftiridina en 20 ml de 2-metoxi-etanol. La mezcla se diluyó con 60 ml de isobutil-metil-cetona y luego se agitó a la temperatura ambiente  
 20 durante 30 h. La resultante suspensión se enfrió a 0°C, se agitó durante 2 h a esa temperatura y luego se filtró. El residuo se lavó con 50 ml de isobutil-metil-cetona y luego se secó en vacío para proporcionar 8,9 g (13,6 mmol, rendimiento: 84%) del compuesto del título.

25 p.f.: 147°C (con sinterización), 180°C (con descomposición)

<sup>1</sup>H-NMR (200 MHz, DMSO): δ = 2,40 (s, 3H); 2,43 (s, 3H);  
 30 3,27 (s, 3H); 3,46 (m, 2H); 3,86 (m, 2H); 3,96 (m, 1H); 4,53 (d, 1H); 4,66 (d, 1H); 7,35-7,49 (m, 8H); 7,90-7,98 (m, 3H); 8,86 (d, 2H)

**Uso de la sal con ácido 1,5-naftaleno disulfónico del**  
 35 **compuesto de la fórmula 1 de acuerdo con el invento**  
**para la preparación del compuesto de la fórmula 1**

Se añadieron 8,9 g (13,6 mmol) de la sal con ácido 1,5-

naftaleno disulfónico de [(7R,8R,9R)-2,3-dimetil-8-hidroxi-7-(2-metoxietoxi)-9-fenil-7,8,9,10-tetrahidro-imidazo-[1,2-h][1,7]-naftiridina] a una solución acuosa diluida de hidróxido de sodio (40,4 mmol). La base libre se extrajo luego con diclorometano y la fase orgánica se concentró en vacío. El residuo se trituro con acetato de etilo para proporcionar 3,4 g (9,3 mmol, rendimiento: 68%) de [(7R,8R,9R)-2,3-dimetil-8-hidroxi-7-(2-metoxietoxi)-9-fenil-7,8,9,10-tetrahidro-imidazo-[1,2-h][1,7]-naftiridina].

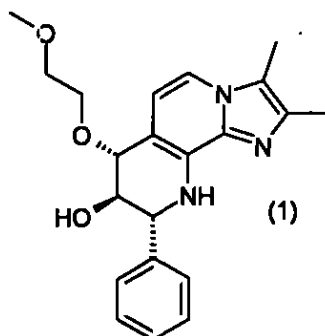
#### Utilidad comercial

La sal por adición de ácido 1,5-naftaleno disulfónico del compuesto de la fórmula 1 es un valioso compuesto intermedio para la preparación del compuesto activo de la fórmula 1 y sus sales, que se describen en la solicitud de patente internacional WO 00/17200.

REIVINDICACIONES

1. La sal por adición de ácido 1,5-naftaleno disulfónico del compuesto de la fórmula 1

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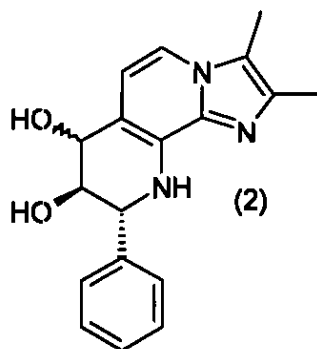


2. La sal por adición de ácido 1,5-naftaleno disulfónico del compuesto de la fórmula 1 de acuerdo con la reivindicación 1, en que la relación molar entre el ácido 1,5-naftaleno disulfónico y el compuesto de la fórmula 1 está situada entre 1 : 1 y 2 : 1.

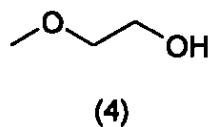
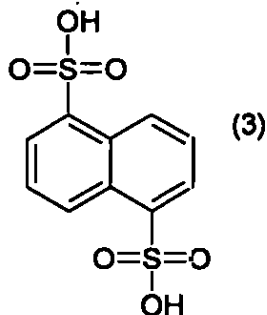
3. La sal por adición de ácido 1,5-naftaleno disulfónico del compuesto de la fórmula 1 de acuerdo con la reivindicación 1, en que la relación molar entre el ácido 1,5-naftaleno disulfónico y el compuesto de la fórmula 1 está situada entre 1 : 1 y 1,2 : 1.

4. El uso de la sal por adición de ácido 1,5-naftaleno disulfónico del compuesto de la fórmula 1 como se reivindica en la reivindicación 1, para la preparación del compuesto de la fórmula 1 y sus sales.

5. Un procedimiento para la preparación de la sal por adición de ácido 1,5-naftaleno disulfónico como se reivindica en la reivindicación 1, que comprende la reacción de un compuesto de la fórmula 2



con el ácido 1,5-naftaleno disulfónico de la fórmula 3 y un alcohol de la fórmula 4



5

y luego su tratamiento.

6. Un procedimiento como se reivindica en la reivindicación 5, que se lleva a cabo en un apropiado disolvente.
7. Un procedimiento como se reivindica en la reivindicación 5, que se lleva a cabo en una cetona seleccionada entre el conjunto formado por acetona, metil-etil-cetona o isobutil-metil-cetona o en un éter seleccionado entre el conjunto formado por dietil-éter, diisopropil-éter o metil-tert.-butil-éter como disolvente.
8. Un procedimiento como se reivindica en la reivindicación 5, que se lleva a cabo en isobutil-metil-cetona como disolvente.

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|-------|-----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| 0     | For receiving Office use only                                                                                                           |                                                                                   |
| 0-1   | International Application No.                                                                                                           |                                                                                   |
| 0-2   | International Filing Date                                                                                                               |                                                                                   |
| 0-3   | Name of receiving Office and "PCT International Application"                                                                            |                                                                                   |
| 0-4   | Form - PCT/RO/101 PCT Request                                                                                                           |                                                                                   |
| 0-4-1 | Prepared Using                                                                                                                          | PCT Online Filing<br>Version 3.50 (Build 0001.162)                                |
| 0-5   | Petition<br>The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty |                                                                                   |
| 0-6   | Receiving Office (specified by the applicant)                                                                                           | European Patent Office (EPO) (RO/EP)                                              |
| 0-7   | Applicant's or agent's file reference                                                                                                   | 1180WOORD01                                                                       |
| I     | Title of invention                                                                                                                      | NOVEL INTERMEDIATE FOR THE PREPARATION OF THERAPEUTICALLY ACTIVE IMIDAZOPYRIDINES |
| II    | Applicant                                                                                                                               |                                                                                   |
| II-1  | This person is:                                                                                                                         | applicant only                                                                    |
| II-2  | Applicant for                                                                                                                           | all designated States except US                                                   |
| II-4  | Name:                                                                                                                                   | ALTANA PHARMA AG                                                                  |
| II-5  | Address:                                                                                                                                | Byk-Gulden-Str. 2<br>78467 Konstanz<br>Germany                                    |
| II-6  | State of nationality                                                                                                                    | DE                                                                                |
| II-7  | State of residence                                                                                                                      | DE                                                                                |
| II-8  | Telephone No.                                                                                                                           | +49 - (0) 7531-84-5264                                                            |
| II-9  | Facsimile No.                                                                                                                           | +49 - (0) 7531-84-5321                                                            |
| II-10 | e-mail                                                                                                                                  | DEKON.IPPA-DE@altanapharma.com                                                    |

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|---------|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| III-1   | Applicant and/or Inventor |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| III-1-1 | This person is:           | applicant and inventor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| III-1-2 | Applicant for             | US only                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| III-1-3 | Inventor for              | AP: (BW GH GM KE LS MW MZ SD SL SZ TZ UG<br>ZM ZW); EA: (AM AZ BY KG KZ MD RU TJ<br>TM); EP: (AT BE BG CH&LI CY CZ DE DK EE<br>ES FI FR GB GR HU IE IT LU MC NL PL PT<br>RO SE SI SK TR); OA: (BF BJ CF CG CI CM<br>GA GN GQ GW ML MR NE SN TD TG); AE AG AL<br>AM AT AU AZ BA BB BG BR BW BY BZ CA CH&<br>LI CN CO CR CU CZ DE DK DM DZ EC EE EG<br>ES FI GB GD GE GH GM HR HU ID IL IN IS<br>JP KE KG KP KR KZ LC LK LR LS LT LU LV<br>MA MD MG MK MN MW MX MZ NA NI NO NZ OM<br>PG PH PL PT RO RU SC SD SE SG SK SL SY<br>TJ TM TN TR TT TZ UA UG US UZ VC VN YU<br>ZA ZM ZW |
| III-1-4 | Name (LAST, First)        | ZIMMERMANN, Peter                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| III-1-5 | Address:                  | Radolfzeller Str. 71a<br>78467 Konstanz<br>Germany                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| III-1-6 | State of nationality      | DE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| III-1-7 | State of residence        | DE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

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|---------|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| III-2   | Applicant and/or inventor | applicant and inventor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| III-2-1 | This person is:           | US only                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| III-2-2 | Applicant for             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| III-2-3 | Inventor for              | AP: (BW GH GM KE LS MW MZ SD SL SZ TZ UG<br>ZM ZW); EA: (AM AZ BY KG KZ MD RU TJ<br>TM); EP: (AT BE BG CH&LI CY CZ DE DK EE<br>ES FI FR GB GR HU IE IT LU MC NL PL PT<br>RO SE SI SK TR); OA: (BF BJ CF CG CI CM<br>GA GN GQ GW ML MR NE SN TD TG); AE AG AL<br>AM AT AU AZ BA BB BG BR BW BY BZ CA CH&<br>LI CN CO CR CU CZ DE DK DM DZ EC EE EG<br>ES FI GB GD GE GH GM HR HU ID IL IN IS<br>JP KE KG KP KR KZ LC LK LR LS LT LU LV<br>MA MD MG MK MN MW MX MZ NA NI NO NZ OM<br>PG PH PL PT RO RU SC SD SE SG SK SL SY<br>TJ TM TN TR TT TZ UA UG US UZ VC VN YU<br>ZA ZM ZW |
| III-2-4 | Name (LAST, First)        | SCHEUFLER, Christian                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| III-2-5 | Address:                  | Lindenstr. 28<br>78234 Engen-Neuhausen<br>Germany                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| III-2-6 | State of nationality      | DE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| III-2-7 | State of residence        | DE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

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|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| III-3   | Applicant and/or Inventor                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| III-3-1 | This person is:                                                                                                                                                                                                                | applicant and inventor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| III-3-2 | Applicant for                                                                                                                                                                                                                  | US only                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| III-3-3 | Inventor for                                                                                                                                                                                                                   | AP: (BW GH GM KE LS MW MZ SD SL SZ TZ UG<br>ZM ZW); EA: (AM AZ BY KG KZ MD RU TJ<br>TM); EP: (AT BE BG CH&LI CY CZ DE DK EE<br>ES FI FR GB GR HU IE IT LU MC NL PL PT<br>RO SE SI SK TR); OA: (BF BJ CF CG CI CM<br>GA GN GQ GW ML MR NE SN TD TG); AE AG AL<br>AM AT AU AZ BA BB BG BR BW BY BZ CA CH&<br>LI CN CO CR CU CZ DE DK DM DZ EC EE EG<br>ES FI GB GD GE GH GM HR HU ID IL IN IS<br>JP KE KG KP KR KZ LC LK LR LS LT LU LV<br>MA MD MG MK MN MW MX MZ NA NI NO NZ OM<br>PG PH PL PT RO RU SC SD SE SG SK SL SY<br>TJ TM TN TR TT TZ UA UG US UZ VC VN YU<br>ZA ZM ZW |
| III-3-4 | Name (LAST, First)                                                                                                                                                                                                             | KOHL, Bernhard                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| III-3-5 | Address:                                                                                                                                                                                                                       | Zum Bruehl 9<br>78465 Konstanz<br>Germany                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| III-3-6 | State of nationality                                                                                                                                                                                                           | DE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| III-3-7 | State of residence                                                                                                                                                                                                             | DE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| III-4   | Applicant and/or Inventor                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| III-4-1 | This person is:                                                                                                                                                                                                                | inventor only                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| III-4-4 | Name (LAST, First)                                                                                                                                                                                                             | MUELLER, Bernd                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| III-4-5 | Address:                                                                                                                                                                                                                       | Buecklestr. 84a<br>78467 Konstanz<br>Germany                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| IV-1    | Agent or common representative; or<br>address for correspondence<br>The person identified below is hereby/<br>has been appointed to act on behalf of<br>the applicant(s) before the competent<br>International Authorities as: | agent                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| IV-1-1  | Name (LAST, First)                                                                                                                                                                                                             | WOLF, Ulrich                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| IV-1-2  | Address:                                                                                                                                                                                                                       | c/o ALTANA Pharma AG, Byk-Gulden-Str. 2<br>78467 Konstanz<br>Germany                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| IV-1-3  | Telephone No.                                                                                                                                                                                                                  | +49 (0) 7531-84-5320                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| IV-1-4  | Facsimile No.                                                                                                                                                                                                                  | +49 (0) 7531-84-5321                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| IV-1-5  | e-mail                                                                                                                                                                                                                         | dekon.ippa-de@altanapharma.com                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| IV-1-6  | Agent's registration No.                                                                                                                                                                                                       | 052382.9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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|                |                                                                                                                                                                                                                                                                                        |                                              |  |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|--|
| <b>V</b>       | <b>DESIGNATIONS</b>                                                                                                                                                                                                                                                                    |                                              |  |
| <b>V-1</b>     | The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents. |                                              |  |
| <b>VI-1</b>    | Priority claim of earlier regional application                                                                                                                                                                                                                                         |                                              |  |
| <b>VI-1-1</b>  | Filing date                                                                                                                                                                                                                                                                            | <b>14 May 2003 (14.05.2003)</b>              |  |
| <b>VI-1-2</b>  | Number                                                                                                                                                                                                                                                                                 | <b>03010785.8</b>                            |  |
| <b>VI-1-3</b>  | Regional Office                                                                                                                                                                                                                                                                        | <b>EP</b>                                    |  |
| <b>VI-2</b>    | Priority document request<br><br>The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):                                                                                     | <b>VI-1</b>                                  |  |
| <b>VII-1</b>   | International Searching Authority Chosen                                                                                                                                                                                                                                               | <b>European Patent Office (EPO) (ISA/EP)</b> |  |
| <b>VII-2</b>   | Request to use results of earlier search; reference to that search                                                                                                                                                                                                                     |                                              |  |
| <b>VII-2-1</b> | Date                                                                                                                                                                                                                                                                                   | <b>08 August 2003 (08.08.2003)</b>           |  |
| <b>VII-2-2</b> | Number                                                                                                                                                                                                                                                                                 | <b>03010785.8</b>                            |  |
| <b>VII-2-3</b> | Country (or regional Office)                                                                                                                                                                                                                                                           | <b>EP</b>                                    |  |
| <b>VIII</b>    | <b>Declarations</b>                                                                                                                                                                                                                                                                    | <b>Number of declarations</b>                |  |
| <b>VIII-1</b>  | Declaration as to the identity of the inventor                                                                                                                                                                                                                                         | <b>-</b>                                     |  |
| <b>VIII-2</b>  | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent                                                                                                                                                               | <b>1</b>                                     |  |
| <b>VIII-3</b>  | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application                                                                                                                                                   | <b>-</b>                                     |  |
| <b>VIII-4</b>  | Declaration of inventorship (only for the purposes of the designation of the United States of America)                                                                                                                                                                                 | <b>1</b>                                     |  |
| <b>VIII-5</b>  | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty                                                                                                                                                                                                         | <b>-</b>                                     |  |

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|             |                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                  |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| VIII-2-1    | <b>Declaration: Entitlement to apply for and be granted a patent</b><br>Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)). In a case where the declaration under Rule 4.17(iv) is not appropriate:<br>Name (LAST, First) | <b>in relation to this international application</b><br><br><b>ALTANA PHARMA AG is entitled to apply for and be granted a patent by virtue of the following:</b> |
| VIII-2-1(i) |                                                                                                                                                                                                                                                                                                                                     | <b>ALTANA PHARMA AG is entitled as employer of the inventor, MUELLER, Bernd</b>                                                                                  |
| VIII-2-1(i) |                                                                                                                                                                                                                                                                                                                                     | <b>ALTANA PHARMA AG is entitled as employer of the inventor, ZIMMERMANN, Peter</b>                                                                               |
| VIII-2-1(i) |                                                                                                                                                                                                                                                                                                                                     | <b>ALTANA PHARMA AG is entitled as employer of the inventor, SCHEUFLE, Christian</b>                                                                             |
| VIII-2-1(i) |                                                                                                                                                                                                                                                                                                                                     | <b>ALTANA PHARMA AG is entitled as employer of the inventor, KOHL, Bernhard</b>                                                                                  |
| VIII-2-1(x) | <b>This declaration is made for the purposes of:</b>                                                                                                                                                                                                                                                                                | <b>all designations except the designation of the United States of America</b>                                                                                   |

PCT REQUEST

Print-Out (Original In Electronic Form)

|            |                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| VIII-4-1   | <p>Declaration: Inventorship (only for the purposes of the designation of the United States of America)<br/>Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:</p> | <p>I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought.</p> <p>This declaration is directed to the international application of which it forms a part (if filing declaration with application).</p> <p>I hereby declare that my residence, mailing address, and citizenship are as stated next to my name.</p> <p>I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications", by application number, country or Member of the World Trade Organization, day, month, and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.</p> |
| VIII-4-1-1 | Prior applications:                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

|              |                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|              |                                                                                                                                                                                                                                           | <p>I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.</p> |
| VIII-4-1-1-1 | Name (LAST, First)                                                                                                                                                                                                                        | ZIMMERMANN, Peter                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| VIII-4-1-1-2 | Residence:<br>(city and either US State, if applicable, or country)                                                                                                                                                                       | Konstanz, Germany                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| VIII-4-1-1-3 | Mailing address:                                                                                                                                                                                                                          | Radolfzeller Str. 71a D-78467 Konstanz Germany                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| VIII-4-1-1-4 | Citizenship:                                                                                                                                                                                                                              | DE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| VIII-4-1-1-5 | Inventor's Signature:<br>(If not contained in the request, or if declaration is corrected or added under Rule 28ter after the filing of the international application. The signature must be that of the inventor, not that of the agent) | /Feter ZIMMERMANN/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| VIII-4-1-1-6 | Date:<br>(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 28ter after the filing of the international application)                                                        | 11 May 2004 (11.05.2004)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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9/10

## PCT REQUEST

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|              |                                                                                                                                                                                                                                           |                                               |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| VIII-4-1-2-1 | Name (LAST, First)                                                                                                                                                                                                                        | SCHEUFLER, Christian                          |
| VIII-4-1-2-2 | Residence:<br>(city and either US State, if applicable, or country)                                                                                                                                                                       | Engen-Neuhausen, Germany                      |
| VIII-4-1-2-3 | Mailing address:                                                                                                                                                                                                                          | Lindenstr. 28 D-78234 Engen-Neuhausen Germany |
| VIII-4-1-2-4 | Citizenship:                                                                                                                                                                                                                              | DE                                            |
| VIII-4-1-2-5 | Inventor's Signature:<br>(If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent) | /Christian SCHEUFLER/                         |
| VIII-4-1-2-6 | Date<br>(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)                                                         | 11 May 2004 (11.05.2004)                      |
| VIII-4-1-3-1 | Name (LAST, First)                                                                                                                                                                                                                        | KOHL, Bernhard                                |
| VIII-4-1-3-2 | Residence:<br>(city and either US State, if applicable, or country)                                                                                                                                                                       | Konstanz, Germany                             |
| VIII-4-1-3-3 | Mailing address:                                                                                                                                                                                                                          | Zum Bruehl 9 D-78465 Konstanz Germany         |
| VIII-4-1-3-4 | Citizenship:                                                                                                                                                                                                                              | DE                                            |
| VIII-4-1-3-5 | Inventor's Signature:<br>(If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent) | /Bernhard KOHL/                               |
| VIII-4-1-3-6 | Date<br>(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)                                                         | 11 May 2004 (11.05.2004)                      |

1180WOORD01

10/10

## PCT REQUEST

Print Out (Original in Electronic Form)

|       |                                                            |                            |                             |
|-------|------------------------------------------------------------|----------------------------|-----------------------------|
| IX    | Check list                                                 | number of sheets           | electronic file(s) attached |
| IX-1  | Request (including declaration sheets)                     | 10                         | ✓                           |
| IX-2  | Description                                                | 7                          | ✓                           |
| IX-3  | Claims                                                     | 2                          | ✓                           |
| IX-4  | Abstract                                                   | 1                          | ✓                           |
| IX-5  | Drawings                                                   | 0                          | ✓                           |
| IX-7  | TOTAL                                                      | 20                         |                             |
|       | Accompanying items                                         | paper document(s) attached | electronic file(s) attached |
| IX-8  | Fee calculation sheet                                      | -                          | ✓                           |
| IX-11 | Copy of general power of attorney                          | -                          | reference no.<br>00026160.2 |
| IX-17 | PCT-SAFE physical media                                    | -                          | -                           |
| IX-19 | Figure of the drawings which should accompany the abstract |                            |                             |
| IX-20 | Language of filing of the international application        | English                    |                             |
| X-1   | Signature of applicant, agent or common representative     | (PKCS7 Digital Signature)  |                             |
| X-1-1 | Name (LAST, First)                                         | WOLF, Ulrich               |                             |
| X-1-2 | Name of signatory                                          |                            |                             |
| X-1-3 | Capacity                                                   |                            |                             |

## FOR RECEIVING OFFICE USE ONLY

|        |                                                                                                                                         |        |
|--------|-----------------------------------------------------------------------------------------------------------------------------------------|--------|
| 10-1   | Date of actual receipt of the purported international application                                                                       |        |
| 10-2   | Drawings:                                                                                                                               |        |
| 10-2-1 | Received                                                                                                                                |        |
| 10-2-2 | Not received                                                                                                                            |        |
| 10-3   | Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application |        |
| 10-4   | Date of timely receipt of the required corrections under PCT Article 11(2)                                                              |        |
| 10-5   | International Searching Authority                                                                                                       | ISA/EP |
| 10-6   | Transmittal of search copy delayed until search fee is paid                                                                             |        |

## FOR INTERNATIONAL BUREAU USE ONLY

|      |                                                                |  |
|------|----------------------------------------------------------------|--|
| 11-1 | Date of receipt of the record copy by the International Bureau |  |
|------|----------------------------------------------------------------|--|

PCT (ANNEX - FEE CALCULATION SHEET)

Print Out (Original in Electronic Form)  
(This sheet is not part of and does not count as a sheet of the international application)

|         |                                                                                                     |                                                    |                     |  |
|---------|-----------------------------------------------------------------------------------------------------|----------------------------------------------------|---------------------|--|
| 0       | For receiving Office use only                                                                       |                                                    |                     |  |
| 0-1     | International Application No.                                                                       |                                                    |                     |  |
| 0-2     | Date stamp of the receiving Office                                                                  |                                                    |                     |  |
|         |                                                                                                     |                                                    |                     |  |
| 0-4     | Form PCT/RO/101 (Annex)<br>PCT Fee Calculation Sheet                                                |                                                    |                     |  |
| 0-4-1   | Prepared Using                                                                                      | PCT Online Filing<br>Version 3.50 (Build 0001.162) |                     |  |
| 0-6     | Applicant's or agent's file reference                                                               | 1130WOORD01                                        |                     |  |
| 2       | Applicant                                                                                           | ALTANA PHARMA AG                                   |                     |  |
| 12      | Calculation of prescribed fees                                                                      | fee amount/multiplier                              | Total amounts (EUR) |  |
| 12-1    | Transmittal fee T                                                                                   | ⇒                                                  | 100                 |  |
| 12-2-1  | Search fee S                                                                                        | ⇒                                                  | 1550                |  |
| 12-2-2  | International search to be carried out by                                                           | EP                                                 |                     |  |
| 12-3    | International filing fee (first 30 sheets) I1                                                       | 902                                                |                     |  |
| 12-4    | Remaining sheets                                                                                    | 0                                                  |                     |  |
| 12-5    | Additional amount (X) 0                                                                             |                                                    |                     |  |
| 12-6    | Total additional amount I2                                                                          | 0                                                  |                     |  |
| 12-7    | I1 + I2 = I                                                                                         | 902                                                |                     |  |
| 12-12   | Electronic Filing reduction (Full) R                                                                | -129                                               |                     |  |
| 12-13   | Total international filing fee (I-R) I                                                              | ⇒                                                  | 773                 |  |
| 12-14   | Fee for priority document                                                                           |                                                    |                     |  |
|         | Number of priority documents requested                                                              | 1                                                  |                     |  |
| 12-15   | Fee per document (X) 30                                                                             |                                                    |                     |  |
| 12-16   | Total priority document fee: P                                                                      | ⇒                                                  | 30                  |  |
| 12-17   | TOTAL FEES PAYABLE (T+S+I+P)                                                                        | ⇒                                                  | 2453                |  |
| 12-19   | Mode of payment                                                                                     | authorization to charge deposit account            |                     |  |
| 12-20   | Deposit account instructions                                                                        |                                                    |                     |  |
|         | The receiving Office                                                                                | European Patent Office (EPO) (RO/EP)               |                     |  |
| 12-20-1 | Authorization to charge the total fees indicated above.                                             | ✓                                                  |                     |  |
| 12-20-2 | Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. | ✓                                                  |                     |  |
| 12-20-3 | Authorization to charge the fee for priority document.                                              | ✓                                                  |                     |  |
| 12-21   | Deposit account No.                                                                                 | 28000022                                           |                     |  |
| 12-22   | Date                                                                                                | 13 May 2004 (13.05.2004)                           |                     |  |
| 12-23   | Name and signature                                                                                  | ALTANA PHARMA AG,<br><br>/Ulrich WOLF/             |                     |  |

PCT (ANNEX - FEE CALCULATION SHEET)

Print Out (Original in Electronic Form)  
(This sheet is not part of and does not count as a sheet of the international application)

REMARKS

|        |                   |                                                                                                                                                                                                                                                                                          |
|--------|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 13-1-1 | Applicant Remarks | It seems to me that the print out does not reflect the data that have been entered into PCT online Filing Software Version 3.50 (Build 0001.162). The following was intended: MUELLER, Bernd is inventor only. He is inventor for all designated states with the exception of US and CA. |
|--------|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|



## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP2004/050780

37

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D471/14

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 C07D

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

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

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

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                           | Relevant to claim No. |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A          | WO 00/17200 A (BYK GULDEN LOMBERG CHEM FAB<br>; SENN BILFINGER JOERG (DE))<br>30 March 2000 (2000-03-30)<br>cited in the application<br>paragraph bridging pages 1 and 2; examples<br>1,5    | 1-8                   |
| A          | WO 01/72756 A (BYK GULDEN LOMBERG CHEM FAB<br>; BUHR WILM (DE); SENN BILFINGER JOERG<br>(DE) 4 October 2001 (2001-10-04)<br>cited in the application<br>third paragraph on page 6; example 5 | 1-8                   |
| A          | US 3 749 721 A (SATZINGER G ET AL)<br>31 July 1973 (1973-07-31)<br>column 1, line 53 - column 1, line 68                                                                                     | 1-8                   |

☐ 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
- "A" document member of the same patent family

Date of the actual completion of the international search

15 September 2004

Date of mailing of the international search report

24/09/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl  
Fax (+31-70) 340-3016

Authorized officer

Wörth, C

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/EP2004/050780

38

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date         |
|-------------------------------------------|---------------------|----------------------------|-----------------------------|
| WO 0017200                                | A                   | 30-03-2000                 | AT 231862 T 15-02-2003      |
|                                           |                     |                            | AU 763463 B2 24-07-2003     |
|                                           |                     |                            | AU 6192099 A 10-04-2000     |
|                                           |                     |                            | BG 105270 A 30-11-2001      |
|                                           |                     |                            | BR 9914044 A 04-12-2001     |
|                                           |                     |                            | CA 2344251 A1 30-03-2000    |
|                                           |                     |                            | CN 1319101 T 24-10-2001     |
|                                           |                     |                            | CZ 20011082 A3 12-09-2001   |
|                                           |                     |                            | DE 69905178 D1 06-03-2003   |
|                                           |                     |                            | DE 69905178 T2 17-07-2003   |
|                                           |                     |                            | DK 1115725 T3 23-06-2003    |
|                                           |                     |                            | EE 200100172 A 17-06-2002   |
|                                           |                     |                            | WO 0017200 A1 30-03-2000    |
|                                           |                     |                            | EP 1115725 A1 18-07-2001    |
|                                           |                     |                            | ES 2191464 T3 01-09-2003    |
|                                           |                     |                            | HK 1038360 A1 16-05-2003    |
|                                           |                     |                            | HR 20010224 A1 30-04-2002   |
|                                           |                     |                            | HU 0102990 A2 28-01-2002    |
|                                           |                     |                            | ID 28896 A 12-07-2001       |
|                                           |                     |                            | JP 2002526499 T 20-08-2002  |
|                                           |                     |                            | NO 20011243 A 12-03-2001    |
|                                           |                     |                            | NZ 510610 A 25-07-2003      |
|                                           |                     |                            | PL 346617 A1 25-02-2002     |
|                                           |                     |                            | PT 1115725 T 30-06-2003     |
|                                           |                     |                            | SI 1115725 T1 30-06-2003    |
|                                           |                     |                            | SK 3992001 A3 03-12-2001    |
|                                           |                     |                            | TR 200100805 T2 21-08-2001  |
|                                           |                     |                            | US 2002169320 A1 14-11-2002 |
|                                           |                     |                            | US 6436953 B1 20-08-2002    |
|                                           |                     |                            | US 2004162310 A1 19-08-2004 |
|                                           |                     |                            | ZA 200102107 A 02-05-2002   |
| WO 0172756                                | A                   | 04-10-2001                 | AU 6016601 A 08-10-2001     |
|                                           |                     |                            | BR 0109483 A 10-06-2003     |
|                                           |                     |                            | CA 2404474 A1 04-10-2001    |
|                                           |                     |                            | CN 1426414 T 25-06-2003     |
|                                           |                     |                            | CZ 20023194 A3 15-01-2003   |
|                                           |                     |                            | WO 0172756 A1 04-10-2001    |
|                                           |                     |                            | EP 1313740 A1 28-05-2003    |
|                                           |                     |                            | HU 0302331 A2 29-12-2003    |
|                                           |                     |                            | JP 2003528878 T 30-09-2003  |
|                                           |                     |                            | NO 20024662 A 27-09-2002    |
|                                           |                     |                            | SK 13852002 A3 04-02-2003   |
|                                           |                     |                            | US 2003125327 A1 03-07-2003 |
|                                           |                     |                            | ZA 200207637 A 08-04-2004   |
| US 3749721                                | A                   | 31-07-1973                 | DE 2011078 A1 16-09-1971    |
|                                           |                     |                            | AT 300818 B 10-08-1972      |
|                                           |                     |                            | BG 17797 A3 25-12-1973      |
|                                           |                     |                            | CH 544097 A 15-11-1973      |
|                                           |                     |                            | CS 167303 B2 29-04-1976     |
|                                           |                     |                            | DK 124130 B 18-09-1972      |
|                                           |                     |                            | GB 1282699 A 19-07-1972     |
|                                           |                     |                            | JP 51004995 B 16-02-1976    |
|                                           |                     |                            | PL 83029 B1 31-12-1975      |
|                                           |                     |                            | RO 57616 A1 15-01-1975      |
|                                           |                     |                            | SU 367602 A3 23-01-1973     |
|                                           |                     |                            | YU 30871 A , B 30-04-1980   |

**PATENT COOPERATION TREATY**  
**PCT**  
**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**  
(Chapter II of the Patent Cooperation Treaty)  
(PCT Article 36 and Rule 70)

|                                                                                            |                                                          |                                              |
|--------------------------------------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------|
| Applicant's or agent's file reference<br>1180WOORD01                                       | <b>FOR FURTHER ACTION</b> See Form PCT/PEA/18            |                                              |
| International application No.<br>PCT/EP2004/050780                                         | International filing date (day/month/year)<br>13.05.2004 | Priority date (day/month/year)<br>14.05.2003 |
| International Patent Classification (IPC) or national classification and IPC<br>C07D471/14 |                                                          |                                              |
| Applicant<br>ALTANA PHARMA AG                                                              |                                                          |                                              |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

a. ☐ sent to the applicant and to the International Bureau) a total of sheets, as follows:

☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 807 of the Administrative Instructions).

☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

b. ☐ (sent to the International Bureau only) a total of (Indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

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

☒ Box No. I Basis of the opinion

☐ Box No. II Priority

☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

☐ Box No. IV Lack of unity of invention

☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

☐ Box No. VI Certain documents cited

☐ Box No. VII Certain defects in the international application

☐ Box No. VIII Certain observations on the international application

|                                                                                                                                                                                                                                                                                     |                                                                                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Date of submission of the demand<br>16.11.2004                                                                                                                                                                                                                                      | Date of completion of this report<br>14.07.2005                                                                                                       |
| Name and mailing address of the international preliminary examining authority:<br> European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Wörth, C<br>Telephone No. +49 89 2399-<br> |

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/EP2004/050780

**Box No. 1 Basis of the report**

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4)
  - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the elements\* of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

1-7 as originally filed

**Claims, Numbers**

1-8 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify)*:
- ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify)*:
- ☐ any table(s) related to sequence listing *(specify)*:

\* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
**PCT/EP2004/050780**

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

|                               |             |     |
|-------------------------------|-------------|-----|
| Novelty (N)                   | Yes: Claims | 1-8 |
|                               | No: Claims  |     |
| Inventive step (IS)           | Yes: Claims | 1-8 |
|                               | No: Claims  |     |
| Industrial applicability (IA) | Yes: Claims | 1-8 |
|                               | No: Claims  |     |

**2. Citations and explanations (Rule 70.7):**

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY  
(SEPARATE SHEET)**

International application No.

PCT/EP2004/050780

**1. Re Item I (*Basis of the report*)**

Reference is made to the following documents:

- D1: WO 00 17200 A (BYK GULDEN LOMBERG CHEM FAB ;SENN BILFINGER JOERG (DE)) 30 March 2000 (2000-03-30)
- D2: WO 01 72756 A (BYK GULDEN LOMBERG CHEM FAB ;BUHR WILM (DE); SENN BILFINGER JOERG) 4 October 2001 (2001-10-04)
- D3: US-A-3 749 721 (SATZINGER G ET AL) 31 July 1973 (1973-07-31)

**2. Re Item V (*Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement*)**

**2.1 Subject-matter**

The application relates to the **1,5-naphthalene disulfonic acid addition salt** of the known gastric acid secretion inhibitor **(7R,8R,9R)-2,3-dimethyl-8-hydroxy-7-(2-methoxyethoxy)-9-phenyl-7,8,9,10-tetrahydro-imidazo(1,2-h)(1,7)naphthyridine**.

The said salt is useful as an intermediate for the preparation of the said gastric acid secretion inhibitor.

**2.2 Novelty**

The subject-matter of the present application differs from

- D1/D2     in view of the **1,5-naphthalene disulfonic acid** addition salt (see D1/D2, passages cited in the search report)
- D3         in view of compound of formula (I)

***The requirements of novelty are met.***

**2.3 Inventive step**

Document D1 is considered as **closest prior art**. This document discloses compounds of formula (I) and some acid addition salts (see paragraph bridging pages 1 and 2). Furthermore discloses document D1 processes for the preparation of compounds of formula (I) (see scheme on page 7 and final product of examples 1 and 5).

**INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY  
(SEPARATE SHEET)**

International application No.

**PCT/EP2004/050780**

In view of this document, the **problem to be solved** can be regarded as the provision of further intermediates for the preparation of compounds of formula (I).

The **solution** provided consists in the 1,5-naphthalene disulfonic salt of claim 1.

The mere provision of a further acid addition salt does not involve an inventive step. However, the provided salts show an **unexpected effect**, which renders the claimed subject-matter **non obvious** over the prior art.

According to the synthesis in the prior art, the final etherification step (see D1, page 7) leads to an epimerisation to an equilibrium of the cis and trans compounds. However, the presence of the said 1,5-naphthalene disulfonic acid in the etherification step yields in a high yield to the **exclusive formation of the desired isoform of formula (I)** as shown in example 1 of the specification.

The disclosure of document D3 related to the precipitation of hexetidine with naphthalene-1,5-disulfonic acid from further reaction impurities does not affect this finding, since this disclosure lacks the critical information for the present much more sophisticated separation problem of cis/trans isomers.

***The requirements of inventive step are met.***

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

## PCT

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

To:

see form PCT/ISA/220

E I N G A N G  
R E C E I V E D

28. Sep. 2004

Gewerblicher  
Rechtsanwalt

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

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

FOR FURTHER ACTION  
See paragraph 2 below

International application No.  
PCT/EP2004/050780

International filing date (day/month/year)  
13.05.2004

Priority date (day/month/year)  
14.05.2003

International Patent Classification (IPC) or both national classification and IPC  
C07D471/14

Applicant  
ALTANA PHARMA AG

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

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

2. FURTHER ACTION

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

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

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

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

Name and mailing address of the ISA:



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu cl  
Fax: +49 89 2399 - 4465

Authorized Officer

Wörth, C

Telephone No. +49 89 2399-8726



**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/EP2004/050780

| Box No. I | Basis of the opinion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1.        | <p>With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.</p> <p><input type="checkbox"/> This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).</p>                                                                                                                                                                                                                                                                                                                                                           |
| 2.        | <p>With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:</p> <p>a. type of material:</p> <p><input type="checkbox"/> a sequence listing</p> <p><input type="checkbox"/> table(s) related to the sequence listing</p> <p>b. format of material:</p> <p><input type="checkbox"/> in written format</p> <p><input type="checkbox"/> in computer readable form</p> <p>c. time of filing/furnishing:</p> <p><input type="checkbox"/> contained in the international application as filed.</p> <p><input type="checkbox"/> filed together with the international application in computer readable form.</p> <p><input type="checkbox"/> furnished subsequently to this Authority for the purposes of search.</p> |
| 3.        | <p><input type="checkbox"/> In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 4.        | <p>Additional comments:</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/EP2004/050780

**Box No. II    Priority**

1. ☒ The following document has not been furnished:
- ☒ copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).
  - ☐ translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(b)).
- Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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

|                               |             |     |
|-------------------------------|-------------|-----|
| 1. Statement                  |             |     |
| Novelty (N)                   | Yes: Claims | 1-8 |
|                               | No: Claims  |     |
| Inventive step (IS)           | Yes: Claims | 1-8 |
|                               | No: Claims  |     |
| Industrial applicability (IA) | Yes: Claims | 1-8 |
|                               | No: Claims  |     |

2. Citations and explanations
- see separate sheet

**1. Re Item I (*Basis of the report*)**

Reference is made to the following documents:

- D1: WO 00 17200 A (BYK GULDEN LOMBERG CHEM FAB ;SENN BILFINGER JOERG (DE)) 30 March 2000 (2000-03-30)  
D2: WO 01 72756 A (BYK GULDEN LOMBERG CHEM FAB ;BUHR WILM (DE); SENN BILFINGER JOERG) 4 October 2001 (2001-10-04)  
D3: US-A-3 749 721 (SATZINGER G ET AL) 31 July 1973 (1973-07-31)

**2. Re Item V (*Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement*)**

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The application relates to the 1,5-naphthalene disulfonic acid addition salt of the known gastric acid secretion inhibitor (7R,8R,9R)-2,3-dimethyl-8-hydroxy-7-(2-methoxyethoxy)-9-phenyl-7,8,9,10-tetrahydro-imidazo(1,2-h)(1,7)naphthyridine.

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The subject-matter of the present application differs from

- D1/D2 in view of the 1,5-naphthalene disulfonic acid addition salt (see D1/D2, passages cited in the search report)  
D3 in view of compound of formula (I)

*The requirements of novelty are met.*

**2.3 Inventive step**

Document D1 is considered as closest prior art. This document discloses compounds of formula (I) and some acid addition salts (see paragraph bridging pages 1 and 2). Furthermore discloses document D1 processes for the preparation of compounds of formula (I) (see scheme on page 7 and final product of examples 1 and 5).

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The disclosure of document D3 related to the precipitation of hexetidine with naphthalene-1,5-disulfonic acid from further reaction impurities does not affect this finding, since this disclosure lacks the critical information for the present much more sophisticated separation problem of cis/trans isomers.

***The requirements of inventive step are met.***

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## REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

|                                                                                                              | USUARIO               | RADICADOR |
|--------------------------------------------------------------------------------------------------------------|-----------------------|-----------|
| <b>PATENTE DE INVENCION</b> ✓                                                                                | ( )                   | ( )       |
| <b>MODELO DE UTILIDAD</b>                                                                                    | ( )                   | ( )       |
| - 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.                                                             | ( )                   | ( )       |
| <b>COMPLETA</b> ( )                                                                                          | <b>INCOMPLETA</b> ( ) | ( )       |
| <b>DISEÑO INDUSTRIAL</b> ( )                                                                                 |                       |           |
| - 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 o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño. | ( )                   | ( )       |
| - Comprobante de pago de las tasas establecidas                                                              | ( )                   | ( )       |
| <b>COMPLETA</b> ( )                                                                                          | <b>INCOMPLETA</b> ( ) | ( )       |
| <b>ESQUEMA DE TRAZADO</b> ( )                                                                                |                       |           |
| - 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.                                                             | ( )                   | ( )       |
| <b>COMPLETA</b> ( )                                                                                          | <b>INCOMPLETA</b> ( ) | ( )       |

Firma Responsable:

Fecha:

52  
50

**REPUBLICA DE COLOMBIA**  
**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

Bogotá,  
2020

Doctor(a)  
ESCOBAR URIBE JIMENA  
Apoderado(a) y/o Representante de  
ALTANA PHARMA A.G.

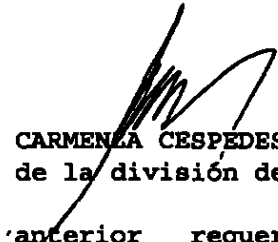
|            |                            |               |
|------------|----------------------------|---------------|
| REFERENCIA | Radicación No.             | 05 96127      |
|            | Solicitud internacional    | EP2004/050780 |
|            | Fecha inicio fase nacional | 14/12/2005    |
|            | Trámite                    | 11            |
|            | Evento                     | 379           |
|            | Actuación                  | 430           |
|            | Oficio No.                 | 13682         |

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

  
ALIX CARMENZA CESPEDES DE VERGEL  
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de  
fecha 23 DIC. 2005  
adpal