



Industria y Comercio
SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

05-17115

21. EXPEDIENTE No.

54. TITULO

MONOETANOSULFONATO DE 3-Z-[1-(4-(N-((4-METIL-PIPERAZINA-1-IL)-

METILCARBONIL)-N-METIL-AMINO)-ANILINO)-1-FENIL-METILEN]-6-METOXICARBONIL-2-

INDOLINONA Y SU UTILIZACION COMO MEDICAMENTOS.

51. CLASIFICACION INTERNACIONAL

A61K31/404, A61P35/04

71. SOLICITANTE

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG.

DOMICILIO

Ingelheim/Rhein, República Federal de Alemania.

74. APODERADO

EMILIO FERRERO

C.C. 438.019 de Usaquén.

22. BOGOTA, D.C.,

23/02/2005.

70
SS


Industria y Comercio

SUPERINTENDENCIA

PETITORIO

SUPERINDUSTRIA Y COMERCIO

Radicación : 85817115 00000000

Folios: 32

Fecha (MM): 2005-02-23 16:41:04

Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 24-02-2005
SOLICITUD DE:

1

☒ Patente de Invención.

☐ Patente de Modelo de Utilidad.

☐ Capítulo I.

☒ Capítulo II.

2

**SOLICITANTE
(71)**

 Nombre: **BOEHRINGER INGELHEIM
PHARMA GMBH & CO. KG**

 sociedad constituida y existente bajo las
leyes de la República Federal de Alemania

 Dirección: 55216 Ingelheim/Rhein,
República Federal de Alemania

 Domicilio: Ingelheim/Rhein,
República Federal de Alemania

IDENTIFICACIÓN

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

3

**REPRESENTANTE
O APODERADO**

 Nombre: **EMILIO FERRERO**
Dirección: **Carrera 4ª. No. 72-35**
Teléfono: **347 36 11**
Fax: **211 88 50**
E-mail: **clientes@camyp.com.**
Domicilio: **Bogotá, Colombia.**
IDENTIFICACIÓN

C.C.

☒

NIT

☐

C.E.

☐

Otro

☐

Cual

 Número **438.019** T.P **31.929**

4

**INVENTOR (ES)
(72)**

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 6. **Frank HILBERG**
Pilgramgasse 18/22,
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 2. **Peter SIEGER**
Wielandstrasse 27,
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 4. **Werner RALL**
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República Federal de Alemania

 6. **Thomas BOCK**
Soeren Norbys Allee 5-1
DK-2300 Copenhagen,
Dinamarca

5

PCT (86)

 Solicitud Internacional No. PCT/EP2003/007822

 Fecha: 18 de Julio de 2003

 Publicación Internacional No. WO 2004/013099 A1

 Fecha: 12 de Febrero de 2004

6

Título (54)
**MONOETANOSULFONATO DE 3-Z-11-(4-(N-(4-METIL-PIPERAZINA-1-IL)-METIL
CARBONIL)-N- METIL-AMINO)-ANILINO)-FENIL-METILEN]-8-METOXICARB NIL-2-
INDOLINONA Y SU UTILIZACIÓN COMO MEDICAMENTO**

7

Clasificación Internacional (51) C07D 209/34
A61K31/404; A61P35/04

8

Prioridad

 SI ☒ NO ☐
(33) País de Origen
DE
(32) Fecha
24 de julio de 2002
(31) Número de Solicitud
102 33 500.1

9

Comprobante de pago No.: 05 - 8.795Fecha: 7 de Febrero de 2005

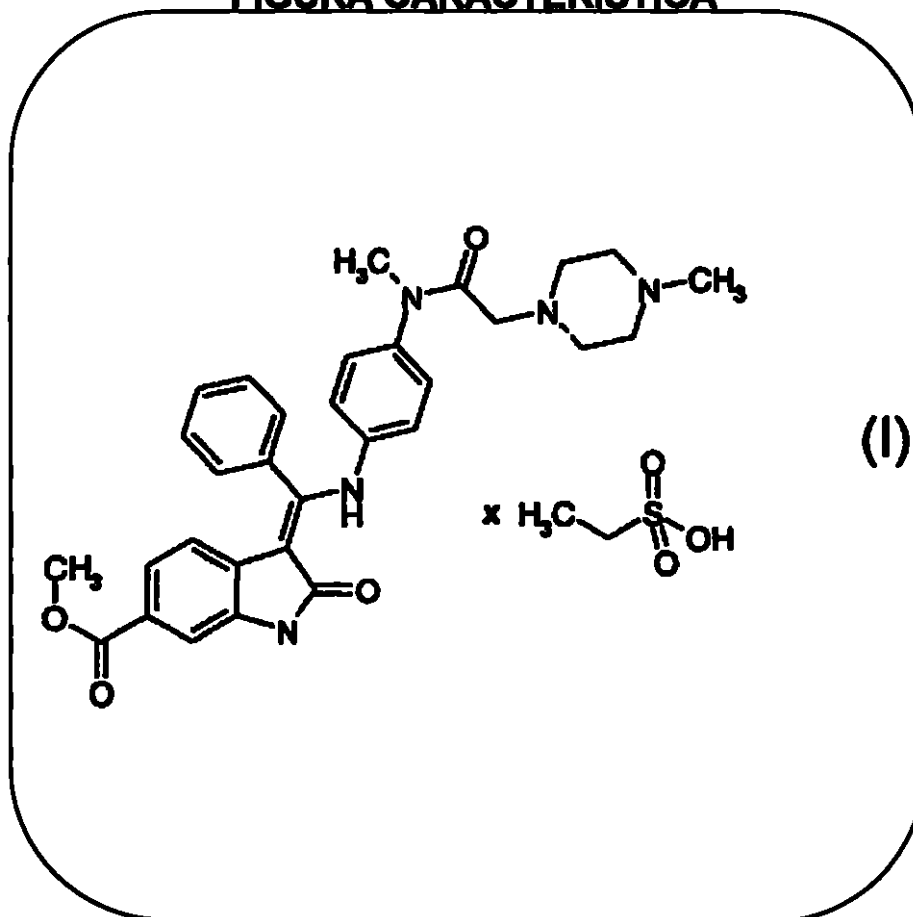
10

Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 443.000.00.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ 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 efectuado por la IPEA.
- ☒ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del 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 12x12
- ☐ 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.
- ☐ Otros

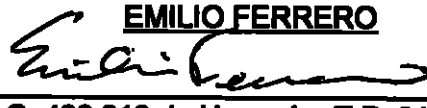
11

FIGURA CARACTERÍSTICA



12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERREROFIRMA: 

C.C. 438.019 de Usaquén T.P. 31.929

PRP

Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of-Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER-OF-ATTORNEY

Yo (nosotros), abajo firmado (s)/I (we), the undersigned

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

domiciliado (s) en/of

55216 Ingelheim, Germany

13736
0564

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª N° 72 35, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial,

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª N° 72 35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate representative occurs, the representation can be taken again by them, secondly by the principal, the first or second alternate depending on the nature of the matter, and its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney to the above named attorneys at law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ

promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

admit the facts of the case, desist, cancel, receive, resign, and ratify done by representatives without a power of attorney.

Dado y firmado hoy/Given and signed this 21st day of March
en/in Ingelheim
por/by _____

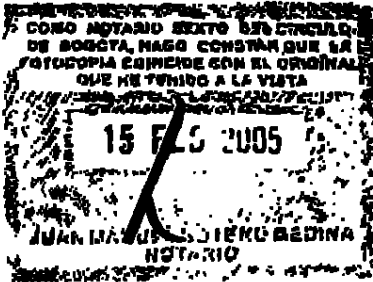
Firma

Signature

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
ppa.


Dr. Heinz-Gerd KLÄS
Head of Patent Department


Dr. Michael KOMPTER
Principal Officer



AUTENTIKACION NOTARIAL (SOCIEDAD)

El infrascrito Notario Certifica: Que la firma que antecede de

1. Heinz-Gerd Kläs

2. Michael Kompter
es auténtica; que el signatario desempeña actualmente el cargo de

de la compañía Boehringer Ingelheim Pharma GmbH & Co. KG

sociedad que actualmente existe y está organizada de acuerdo a las leyes de Alemania

que la dirección de la compañía es 55216 Ingelheim am Rhein Binger Straße 173

y que el signatario tiene facultad para otorgar este documento.

Todos los hechos anteriores le constan por haber examinado los documentos respectivos y de todo da fe.

Dado y firmado en Ingelheim am Rhein

21 MARZO 2003

NOTARIAL AUTHENTICATION (COMPANY)

The undersigned Notary certifies: That the preceding signature of 1.Mr.Dr.Heinz-Gerd Kläs and 2.Mr.Dr.Michael Kompter

is authentic, that the signatory currently acts in the position of procurists

of the company Boehringer Ingelheim Pharma GmbH & Co. KG

a company currently existing and organized under the laws of Germany

that the address is 55216 Ingelheim am Rhein Binger Straße 173

and that the signatory has the power to grant this document.

The Notary Public is aware and attests to the above facts upon examination of the corresponding documents.

Given and signed in Ingelheim am Rhein

On the 21th day of March 2003

Notary Public
(Signature-seal)



Apostille

(Convention de La Haye du 5 octobre 1961)

1. Land Bundesrepublik Deutschland

Diese öffentliche Urkunde

2. ist unterschrieben von

Alfred Fuchs

3. in seiner Eigenschaft als Notar

4. sie ist versehen mit dem Dienstsiegel des Alfred Fuchs - Notar in Ingelheim am Rhein

Bestätigt

Mainz, den 24.03.03

5. in Mainz 6. am 24.03.03

7. durch den Präsidenten des Landgerichts

8. unter Nr. 269/2003

9. Stempel/Siegel 10. Unterschrift

In Vertretung:

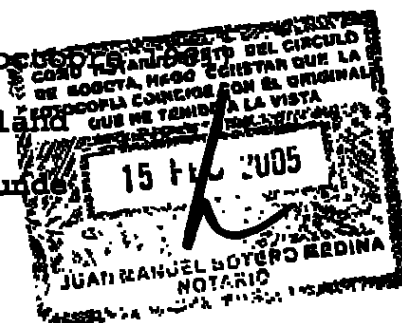
KOSTENRECHNUNG:

Gebühr für die
Erteilung der
Legalisation
Wert: EUR 20.000,00
JVKostO v.26.7.57
i.V.m. § 45 KostO
Gebühr: EUR 18,00

Justizsekretärin



Dr. Harald Binger
(Dr. Harald Binger)
Vizepräsident



5

TRADUCCION OFICIAL No. 9468

de un documento escrito en Alemán, efectuada por Luz Arriaga de Herber, resolución del Ministerio de Justicia 599 del 6 de marzo 1978.-

Traducción de los sellos y autenticaciones en Alemán que aparecen en el documento de representación y poder, escrito en español e inglés, por medio del cual la firma Boehringer Ingelheim Pharma GmbH & Co. KG, domiciliada en D-55216 Ingelheim am Rhein, Alemania, otorga poder a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4 No. 72-35, Bogotá, Colombia. Dado y firmado el 21 de marzo 2003 en Ingelheim am Rhein por los señores Dr. Heinz-Gerd KLÄS y Dr. Michael KOMPTER, representantes legales de la mencionada firma.

Sigue autenticación notarial en español e inglés de los antecedentes por el notario de Ingelheim am Rhein, Alfred Fuchs, el 21 de marzo 2003, bajo el No. 571/2003.

COSTAS:

Derechos de legalización

Valor: EUROS 20.000,--

LUZ ARRIAGA DE HERBER
TRADUCCION OFICIAL
15 FEB 2005
JUAN MANUEL BUSTOZ MEDINA
NOTARIO

JVKostO del 26.7.57 en combinación con Art. 45 KostO

Derechos: EUROS 18,00

Mainz, 24.03.03

Fdo.: ilegible,

Secretaría de justicia

APOSTILLA

(Convention de La Haye du 5 octobre 1961)

1. País: República Federal de Alemania

Este documento público

2. Ha sido firmado por el notario Alfred Fuchs

3. Actuando en calidad de notario

4. Lleva el sello oficial del notario de Ingelheim am Rhein,
Alfred Fuchs

Certificado

5. en Mainz

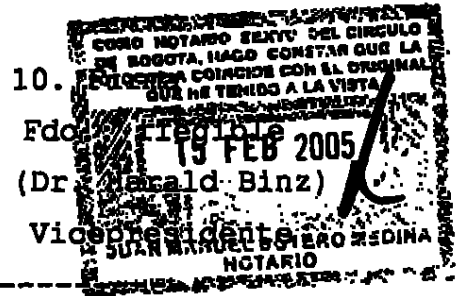
6. el 24.03.03

7. por el Presidente del Tribunal Regional

8. bajo el No 269/2003 /

9. Sello

Tribunal Regional de Mainz



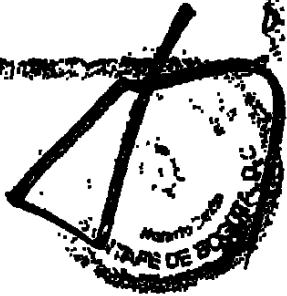
ES TRADUCCION FIEL Y COMPLETA, de la cual se deja copia en los
archivos de estas oficinas para su confrontación.

Bogotá, 7 de abril 2003

[Handwritten signature]
Luz A. ...
...
...
...
...

17

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA. HAGO CONSTAR QUE LAS FIRMA(S) DE
Luz Arriaga de Herber
CONCORDA CON LA FIRMA REGISTRADA POR
EL (LOS) EN ESTA NOTARIA
SANTAFE DE BOGOTA, 09 ABR 2002



NO SE ASUME
RESPONSABILIDAD DEL TEXTO
7003 APR - 6 11:08
JEFE DE CALIFICACIONES
BOGOTA D.C.

MINISTERIO DE
RELACIONES EXTERIORES

1924542
Arriaga de H
CUYA FIRMA DE: [illegible] EN EL
DOCUMENTO D: [illegible] SE PUEDE
LAS FUNCIONES INDICADAS

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CONCORDE CON EL ORIGINAL QUE SE TRUENO A LA VISTA
5 FEB 2005

CAVELIER

374

ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 8 - COLOMBIA

CESION

ASSIGNMENT

Yo, (nosotros) abajo firmado (s)

1. Gerald J. ROTH
2. Peter SIEGER
3. Guenter LINZ
4. Werner RALL
5. Frank HILBERG
6. Thomas BOCK

Domiciliado(s)

en

1. Akazienweg 47, 88400 Biberach, Germany
2. Klingenaecker 7, 88441 Mittelbiberach, Germany
3. Eschenweg 6, 88441 Mittelbiberach, Germany
4. Beethovenstrasse 33, 88441 Mittelbiberach, Germany
5. Pilgramgasse 18/22, 1050 Wien, Austria
6. Soeren Norbys Allee 5-1, 2300 Copenhagen, Denmark

Declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención *monoethanesulphonate of 3-2-[1-(4-methyl-piperazin-1-yl)-methyl-carbonyl]-N-methyl-amino-anilino-1-phenyl-methylene-6-methoxycarbonyl-2-indolone* *utilización como medicamento*

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad

Boehringer Ingelheim Pharma GmbH & Co. KG

constituida y existente de conformidad con las leyes de

Alemania

domiciliada en Binger Strasse 173, 55216 Ingelheim, Alemania

todos los derechos inherentes a dicha invención y que la citada

Compañía queda facultada para solicitar en su nombre la patente de invención correspondiente en la República de Colombia.

I (we), the undersigned

1. Gerald J. ROTH
2. Peter SIEGER
3. Guenter LINZ
4. Werner RALL
5. Frank HILBERG
6. Thomas BOCK

of

1. Akazienweg 47, 88400 Biberach, Germany
2. Klingenaecker 7, 88441 Mittelbiberach, Germany
3. Eschenweg 6, 88441 Mittelbiberach, Germany
4. Beethovenstrasse 33, 88441 Mittelbiberach, Germany
5. Pilgramgasse 18/22, 1050 Wien, Austria
6. Soeren Norbys Allee 5-1, 2300 Copenhagen, Denmark

state(s) under oath to be sole and true inventor(s) of the invention: "3-2-[1-(4-(4-Methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino-anilino]-1-phenyl-methylene-6-methoxycarbonyl-2-indolone-monoethanesulphonate and the use thereof as a pharmaceutical composition"

state as well, that assign, without reservations or limitations in favour of Boehringer Ingelheim Pharma GmbH & Co. KG

a corporation constituted and existing in conformity with the laws of

Germany

domiciled in Binger Strasse 173, 55216 Ingelheim, Germany

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent invention, in the Republic of Colombia

Dado y firmado hoy/Given and signed this

en/in

Firma/Signature

Wien, am 27.12.2004

Gerald J. ROTH

Peter SIEGER

Guenter LINZ

Werner RALL

Frank HILBERG

Thomas BOCK



CERTIFICACIÓN NOTARIAL (INDIVIDUO)

A los _____ días del mes de _____
de 200 ____ Ante mí, Notario Público de

compareció(eron) personalmente _____

a quien(es) doy fe de conocer y me consta que es(son) la(s)
persona(s) firmante(s) del documento que precede, y quien(es)
tiene(n) capacidad legal para otorgarlo

NOTARIAL CERTIFICATION (INDIVIDUAL)

On this _____ day of _____
200 ____ before me, a Notary Public of

personally appeared _____

to me known, and known to me to be the person(s) who executed
that foregoing document, and who has(have) legal capacity to
execute it.

NOTARIO PÚBLICO-NOTARY PUBLIC

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

- 1. Country:
This public document
- 2. has been signed by
- 3. acting in the capacity of
- 4. bears the seal/stamp of

Certified

- 5. at 6. the
- 7. by
- 8. No.
- 9. Seal/stamp 10. Signature

.....

Gebühr in Höhe von €13,00
gem. § 14 TP 13 GebG idF
BGBl. I 144/2001 entrichtet.

B.R.Zl.: 911/2004

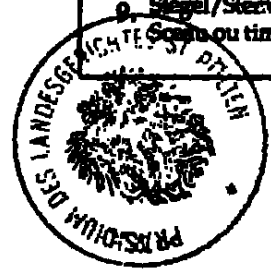
Ich bestätige die Echtheit der Unterschrift des Herrn Doktor Frank Hilberg,
geboren am 30.10.1956 (dreißigsten Oktober neunzehnhundertsechsfundfünfzig),
Diplom-Biochemiker, Pilgramgasse 18/22, A-1050 Wien. _____
Pöggstall, am 27.12.2004 (siebenundzwanzigsten Dezember zweitausendvier). _____



[Handwritten Signature]
Dr. Christoph VÖLKE
öffentlicher Notar

Geb. 13,00 €
entrichtet

Apostille (Convention de la Haye du 5 octobre 1961)	
1. Land:	ÖSTERREICH
2. Pays:	
Dieser öffentliche Urkunde / Le présent document officiel	
3. in dem Namen:	Dr. Christoph Völkel
4. ist von:	öffentlicher Notar
5. ist von:	Notar
6. am:	28. 12. 2004
7. durch den Präsidenten:	
8. unter Nr.:	3v 4804-25/04
9. durch den Präsidenten:	
10. Unter schrift:	
Für den Präsidenten	



[Handwritten Signature]
VB HALTER TITINA

TRADUCCION OFICIAL No. 10587

de un documento escrito en Alemán, efectuada por Luz Arriaga de Herber, resolución del Ministerio de Justicia 599 del 6 de marzo 1978.-

Traducción de los sellos y autenticaciones en alemán que aparecen a continuación de un documento de Cesión, escrito en español e inglés, por medio del cual

- 1. Gerald J. ROTH**
- 2. Peter SIEGER**
- 3. Guenter LINZ**
- 4. Werner RALL**
- 5. Frank HILBERG**
- 6. Thomas BOCK**

domiciliados en

- 1. Akazienweg 47, 88400 Biberach, Alemania**
- 2. Klingenaecker 7, 88441 Mittelbiberach, Alemania**
- 3. Eschenweg 6, 88441 Mittelbiberach, Alemania**
- 4. Beethovenstrasse 33, 88441 Mittelbiberach, Alemania**
- 5. Pilgramgasse 18/22, 1050 Viena, Austria**
- 6. Soeren Norbys Allee 5-1, 2300 Copenhagen, Dinamarca**

declaran bajo juramento ser únicos y verdaderos inventores de la invención "Monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-1-piperazin-1-il)-metilcarbonil)-N-metilamino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-Indolna y su utilización como medicamento" y declaran así mismo que ceden y transfieren sin limitación a favor de la sociedad Boehringer Ingelheim Pharma GmbH & Co. KG., constituida y existente de conformidad con las leyes de Alemania, domiciliada en Binger Strasse 173, 55216 Ingelheim, Alemania, todos los derechos inherentes a dicha invención y que la citada compañía queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia. Hay una firma ilegible del señor Frank Hilberg.

LUZ ARRIAGA DE HERBER
TRADUCTORA E INTERPRETE OFICIAL

Resolución No. 599 Minjusticia

[Cancelados derechos por valor de € 13,00
Seg. Art. 14 TP 13 Ley de derechos en la
Versión de la Gaceta oficial I 144/2001.]

Protocolo notarial I Nr.911/2004

certificó la autenticidad de la firma del señor Dr. Frank Hillberg, nacido el 30.10.1956
(30 de octubre de mil novecientos cincuenta y seis), Dipl.-Bioquímico, domiciliado en
Pilgramgasse 18/22,
A-1050 Viena.

Pöggstall, 27.12. 2004 (veintisiete de diciembre de dos mil cuatro).

Dr. Christoph Völk, notario público, Pöggstall
(sello redondo en tinta)
Fdo.: firma ilegible
Notario público
(Hilo y oblaa notarial)

APOSTILLE
(Convention de La Haya du 5 octobre 1961)

1. País: AUSTRIA

Este documento público

2. Ha sido firmado por el Dr. Christoph VÖLK

3. Actuando en calidad de notario público

4. Lleva el sello oficial del notario

Certificado

5. en St. Pölten

7. por el Presidente

9. Sello

Tribunal Regional St. Pölten

6. el 28 de diciembre 2004

8. bajo el No. Jv 4904-25/04

10. Firma

Fdo.: ilegible

por el presidente:

VB HALLER BETTINA

ES TRADUCCION FIEL Y COMPLETA, de la cual se deja copia en los archivos de
estas oficinas para su confrontación.

Bogotá, 18 de febrero de 2005

C. 2595

LUZ ARRIAGA DE HEREDIA
TRADUCTORA E INTERPRETE OFICIAL
Luz Arriaga de Heredia
Resolución No.593 Minjusticia

MINISTERIO DE RELACIONES
EXTERIORES

203 892129
Dm 3015

COTA FIRMA APARECE EN EL
DOCUMENTO DESEMPENA
LAS FUNCIONES INDICADAS

NO SE ASUME
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2005 FEB 23 P 1:26

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EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 8 - COLOMBIA

374

25

12

CESION

ASSIGNMENT

Yo, (nosotros) abajo firmado (s)

I (we), the undersigned

- 1. Gerald J. ROTH
- 2. Peter SIEGER
- 3. Guenter LINZ
- 4. Werner RALL
- 5. Frank HILBERG
- 6. Thomas BOCK

- 1. Gerald J. ROTH
- 2. Peter SIEGER
- 3. Guenter LINZ
- 4. Werner RALL
- 5. Frank HILBERG
- 6. Thomas BOCK

Domiciliado(s)

of

- 1. Akazienweg 47, 88400 Biberach, Germany
- 2. Klingenaeker 7, 88441 Mittelbiberach, Germany
- 3. Eschenweg 6, 88441 Mittelbiberach, Germany
- 4. Beethovenstrasse 33, 88441 Mittelbiberach, Germany
- 5. Pilgramgasse 18/22, 1050 Wien, Austria
- 6. Soeren Norbys Allee 5-1, 2300 Copenhagen, Denmark

- 1. Akazienweg 47, 88400 Biberach, Germany
- 2. Klingenaeker 7, 88441 Mittelbiberach, Germany
- 3. Eschenweg 6, 88441 Mittelbiberach, Germany
- 4. Beethovenstrasse 33, 88441 Mittelbiberach, Germany
- 5. Pilgramgasse 18/22, 1050 Wien, Austria
- 6. Soeren Norbys Allee 5-1, 2300 Copenhagen, Denmark

Declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención: *monoethanesulphonate de 3-2-
3-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino-anilino-1-phenyl-methylene-6-methoxycarbonyl-2-indolone y su utilización como medicamento*

state(s) under oath to be sole and true inventor(s) of the invention: "3-Z-[1-(4-(N-((4-Methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene-6-methoxycarbonyl-2-indolone-monoethanesulphonate and the use thereof as a pharmaceutical composition"

declaro(amos) así mismo que cedo(amos) y transfiero(emos), sin limitación, a favor de la sociedad

state as well, that assign, without reservations or limitations in favour of Boehringer Ingelheim Pharma GmbH & Co. KG

Boehringer Ingelheim Pharma GmbH & Co. KG

a corporation constituted and existing in conformity with the laws of Germany

constituida y existente de conformidad con las leyes de Alemania

domiciliada en Binger Strasse 173, 55216 Ingelheim, Alemania

domiciled in Binger Strasse 173, 55216 Ingelheim, Germany

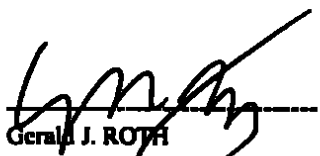
todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente de invención correspondiente en la República de Colombia.

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent invention, in the Republic of Colombia

Dado y firmado hoy/Given and signed this

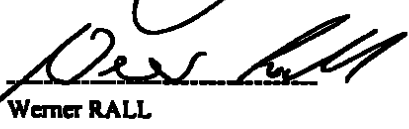
en/in

Firma/Signature

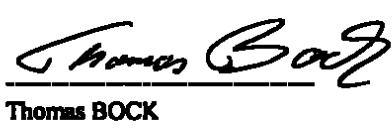

Gerald J. ROTH


Peter SIEGER


Guenter LINZ


Werner RALL


Frank HILBERG


Thomas BOCK

13

CERTIFICACIÓN NOTARIAL (INDIVIDUO)

A los _____ días del mes de _____
de 200 ____ Ante mí, Notario Público de _____

compareció(eron) personalmente _____

a quien(es) doy fe de conocer y me consta que es(son) la(s)
persona(s) firmante(s) del documento que precede, y quien(es)
tiene(n) capacidad legal para otorgarlo

NOTARIAL CERTIFICATION (INDIVIDUAL)

On this _____ day of _____
200 ____ before me, a Notary Public of _____

personally appeared _____

to me known, and known to me to be the person(s) who executed
that foregoing document, and who has(have) legal capacity to
execute it.

NOTARIO PÚBLICO-NOTARY PUBLIC

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

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This public document
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- 3. acting in the capacity of
- 4. bears the seal/stamp of

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- 5. at 6. the
- 7. by
- 8. No.
- 9. Seal/stamp 10. Signature

.....

Notariat I Zeppelinring 56, 88400 Biberach
Telefon 07351/1803-10 Fax 07351/1803-60

Unterschriftsbeglaubigung:

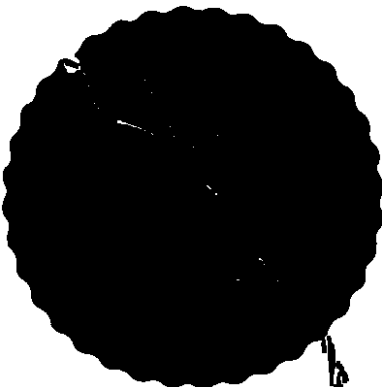
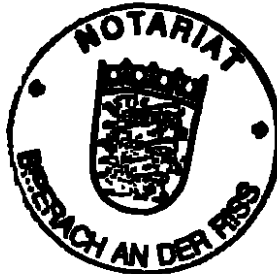
Vorstehende, vor mir vollzogene Unterschriften von

1. Herrn Dr. Gerald Roth, Diplom-Chemiker, geb. am 05.08.1966,
wohnhaft in Akazienweg 47, 88400 Biberach,
-persönlich bekannt-,
2. Herrn Dr. Peter Sieger, Chemiker, geb. am 09.09.1963,
wohnhaft in Klingenäcker 7, 88441 Mittelbiberach,
-persönlich bekannt-,
3. Herrn Dr. Günter Linz, Diplom-Chemiker, geb. am 17.08.1957,
wohnhaft in Eschenweg 6, 88441 Mittelbiberach,
-persönlich bekannt-,
4. Herrn Werner Rall, Chemielaborant, geb. am 05.02.1949,
wohnhaft in Beethovenstr. 33, 88441 Mittelbiberach,
-persönlich bekannt-,
5. Herrn Dr. Thomas Bock, Apotheker, geb. am 24.06.1965,
wohnhaft in Soeren Norbys Allee 5-1, 2300 Kopenhagen (Dänemark),
-persönlich bekannt-,

beglaubige ich hiermit.

Biberach, den 07.01.2005
Notariat Biberach

Fuchsbachwanz
Notar



Apostille (Convention de La Haye du 5 octobre 1961)	
1. Land: Bundesrepublik Deutschland	
Diese öffentliche Urkunde	
2. ist unterschrieben von	<i>Notar Fuchsbachwanz</i>
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4. sie ist versehen mit dem Siegel/Stempel des	<i>Notariats Biberach</i>
Bestätigt	
5. In Ravensburg	6. am <i>1.8. Jan. 05</i>
7. durch den Präsidenten des Landgerichts	
8. unter Nr. 913 a - <i>28/05</i>	
9. Siegel/Stempel	10. Unterschrift
	<i>Dr. Steinle</i>

TRADUCCION OFICIAL No. 10588

de un documento escrito en Alemán, efectuada por Luz Arriaga de Herber, resolución del Ministerio de Justicia 599 del 6 de marzo 1978.-

Traducción de los sellos y autenticaciones en alemán que aparecen a continuación de un documento de Ceslón, escrito en español e inglés, por medio del cual los señores

1. Gerald J. ROTH
2. Peter SIEGER
3. Guenter LINZ
4. Werner RALL
5. Frank HILBERG
6. Thomas BOCK

domiciliados en

1. Akazienweg 47, 88400 Biberach, Alemania
2. Klingensacker 7, 88441 Mittelbiberach, Alemania
3. Eschenweg 6, 88441 Mittelbiberach, Alemania
4. Beethovenstrasse 33, 88441 Mittelbiberach, Alemania
5. Pilgramgasse 18/22, 1050 Viena, Austria
6. Soeren Norbys Allee 5-1, 2300 Copenhagen, Dinamarca

declaran bajo juramento ser únicos y verdaderos inventores de la invención "Monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-1-piperazin-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-indolina y su utilización como medicamento" y declaran así mismo que ceden y transfieren sin limitación a favor de la sociedad Boehringer Ingelheim Pharma GmbH & Co. KG., constituida y existente de conformidad con las leyes de Alemania, domiciliada en Binger Strasse 173, 55216 Ingelheim, Alemania, todos los derechos inherentes a dicha invención y que la citada compañía queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia. Hay cinco firmas legibles de los señores Roth, Sieger, Linz, Rall y Bock.

Protocolo notarial | Nr. 6/2005

Notaría | Zeppelinger 56, 88400

Tel. 07351/1803-10 Fax 07351/1803-80

AUTENTICACION DE FIRMA

Certifico la autenticidad de la firma antecedente, puesta ante mí, por los señores

1. Dr. Gerald Roth, Diplom-Químico, nacido el 05.08.1966,
domiciliado en Akazienweg 47, 88400 Biberach,
-a quien conozco en persona-,

LUZ ARRIAGA DE HERBER
TRADUCTORA E INTERPRETE OFICIAL

Resolución No. 599 Minjusticia

2. Dr. Peter Sieger, Químico, nacido el 09.09.1963, domiciliado en Klingenhacker 7, 88441 Mittelbiberach, -a quien conozco en persona-,
3. Dr. Günter Linz, Diplom-Químico, nacido el 17.08.1957, domiciliado en Eschenweg 6, 88441 Mittelbiberach, -a quien conozco en persona-,
4. Werner Rall, Asistente químico, nacido el 05.02.1949, domiciliado en Beethovenstr. 33, 88441 Mittelbiberach, -a quien conozco en persona-,
5. Dr. Thomas Bock, Farmacéuta, nacido el 24.06.1965, domiciliado en Soeren Norbys Allee 5-I, 2300 Kopenhagen (Dänemark), -a quien conozco en persona-,

Biberach, 07.01.2005
Notaría Biberach

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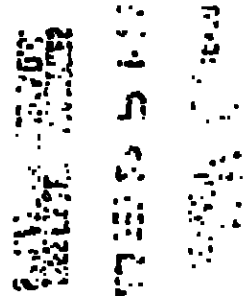
Fuchsschwanz

Notario

(Hilo y oblea notarial en relieve)

(sello redondo en tinta)

Notaría - Biberach an der Riss



APOSTILLA
(Convention de La Haya du 5 octobre 1961)

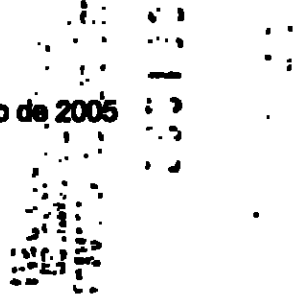
1. País: República Federal de Alemania
Este documento público
2. Ha sido firmado por el notario Fuchsschwanz
3. Actuando en calidad de notario público
4. Lleva el sello oficial del notario de Biberach

Certificado

5. en Ravensburg
7. por el Presidente del Tribunal Regional
8. bajo el No 910 a - 28/05
9. Sello
Tribunal Regional de Ravensburg

6. el 18. de enero de 2005

10. Firma
Fdo.: ilegible
Dr. Steinle



ES TRADUCCION FIEL Y COMPLETA, de la cual se deja copia en los archivos de estas oficinas para su confrontación.

Bogotá, 18 de febrero de 2005
C. 3122

LIZ ARRIAGA DE HERNANDEZ
TRADUCTORA E INTERPRETE OFICIAL

Resolución No. 599 Min. Justicia

MINISTERIO DE RELACIONES
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JS
092130
Dr. 1305
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 FEB 23 P 1 26

ues
JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

U 12

(19) World Intellectual Property
Organization
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12 February 2004 (12.02.2004)

PCT

(10) International Publication Number
WO 2004/013099 A1

(51) International Patent Classification⁷: C07D 209/34,
A61K 31/404, A61P 35/04

A-1050 Wien (AT). BOCK, Thomas [DE/DK]; Soeren
Norbys Allee 5-1, DK-2300 Copenhagen (DK).

(21) International Application Number:
PCT/EP2003/007822

(74) Common Representative: BOEHRINGER INGEL-
HEIM PHARMA GMBH & CO. KG; 55216 Ingel-
heim/Rhein (DE).

(22) International Filing Date: 18 July 2003 (18.07.2003)

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CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GR, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,
SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
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European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*):
BOEHRINGER INGELHEIM PHARMA GMBH
& CO. KG [DE/DE]; 55216 Ingelheim/Rhein (DE).

(72) Inventors; and

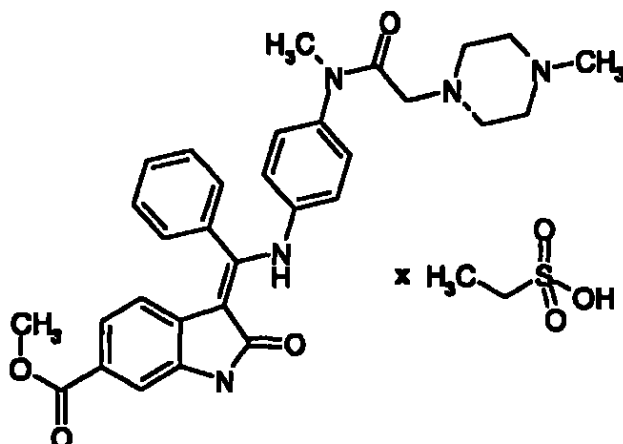
(75) Inventors/Applicants (*for US only*): ROTH, Gerald,
Jürgen [DE/DE]; Akazienweg 47, 88400 Biberach (DE).
SIEGER, Peter [DE/DE]; Wielandstrasse 27, 88441
Mittelbiberach (DE). LINZ, Guenter [DE/DE]; Eschen-
weg 6, 88441 Mittelbiberach (DE). BALL, Werner
[DE/DE]; Beethovenstrasse 33, 88441 Mittelbiberach
(DE). HILBERG, Frank [DE/AT]; Pilgrimgasse 18/22,

Published:

— with international search report

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

(54) Title: 3-Z-[1-(4-(N-((4-METHYL-PIPERAZIN-1-YL)-METHYLCARBONYL)-N-METHYL-AMINO)-ANILINO)-1-PHENYL-METHYLENE]-6-METHOXYCARBONYL-2-INDOLINONE-MONOTHANESULPHONATE AND THE USE THEREOF AS A PHARMACEUTICAL COMPOSITION

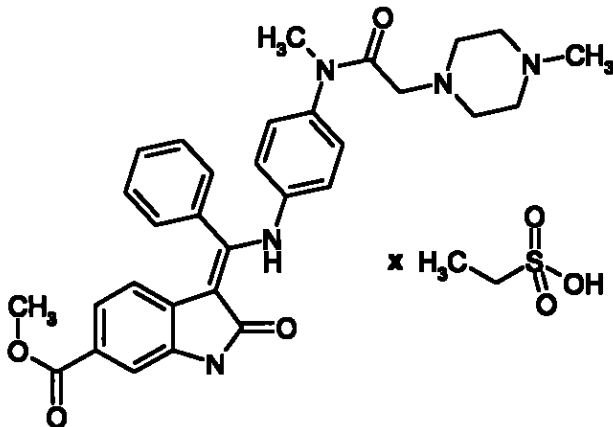


(57) Abstract: The present invention relates to the compound 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monothanesulphonate of formula (I) and the use thereof as a pharmaceutical composition.

3-Z-[1-(4-(N-((4-Methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-Indolinone-monoethanesulphonate
and the use thereof as a pharmaceutical composition

The present invention relates to the compound 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-Indolinone-monoethanesulphonate of formula I and the use thereof in a pharmaceutical composition.

Formula I:



Background to the Invention

A number of 2-indolinone derivatives are already known in the prior art. Thus, for example, International Patent Application WO 01/27081 discloses 2-indolinone derivatives which have valuable pharmacological properties.

Like the 2-Indolinone derivatives mentioned in the prior art, the compound of formula I also has, in particular, an inhibiting effect on various kinases, particularly receptor tyrosine kinases such as VEGFR1, VEGFR2, VEGFR3, PDGFR α , PDGFR β , FGFR1, FGFR3, EGFR, HER2, c-Kit, IGF1R, Flt-3 and HGFR, and on the proliferation of

cultivated human cells, particularly endothelial cells, e.g. in angiogenesis, but also on the proliferation of other cells, particularly tumour cells.

5 The pharmacologically valuable properties of the indolnones disclosed in the art and mentioned above constitute the basic prerequisite for effective use of the compounds as pharmaceutical compositions. An active substance must in any case satisfy additional requirements in order to be accepted for use as a drug. These parameters are largely connected with the physicochemical nature of the active substance.

10

Without being restrictive, examples of these parameters are the stability of effect of the starting substance under various environmental conditions, the stability during production of the pharmaceutical formulation and stability in the final compositions of the drug. The pharmaceutically active substance used to prepare the pharmaceutical compositions should therefore have great stability which is ensured even under all kinds of environmental conditions. This is absolutely essential to prevent pharmaceutical compositions being used which contain breakdown products, for example, in addition to the active substance itself. In such a case the content of active substance present in the pharmaceutical formulation might be lower than specified.

20

The absorption of moisture reduces the content of pharmaceutically active substance as a result of the increased weight caused by the uptake of water. Pharmaceutical compositions with a tendency to absorb moisture have to be protected from moisture during storage, e.g. by the addition of suitable drying agents or by storing the drug in an environment where it is protected from moisture. In addition, the uptake of moisture may reduce the content of pharmaceutically active substance during manufacture if the pharmaceutical substance is exposed to the environment without being protected from moisture in any way. Preferably, therefore, a pharmaceutically active substance should be only slightly hygroscopic.

30

As the crystal modification of an active substance is important to the reproducible active substance content of a preparation, there is a need to clarify as far as possible any existing polymorphism of an active substance present in crystalline form. If there are different polymorphic modifications of an active substance care must be taken to ensure

that the crystalline modification of the substance does not change in the pharmaceutical preparation later produced from it. Otherwise, this could have a harmful effect on the reproducible potency of the drug. Against this background, active substances characterised by only slight polymorphism are preferred.

5

Another criterion which may be of exceptional importance under certain circumstances depending on the choice of formulation or the choice of manufacturing process is the solubility of the active substance. If for example pharmaceutical solutions are prepared (e.g. for infusions) it is essential that the active substance should be sufficiently soluble
10 In physiologically acceptable solvents. It is also very important for drugs which are to be taken orally that the active substance should be sufficiently soluble.

The problem of the present invention is to provide a pharmaceutically active substance which not only is characterised by high pharmacological potency but also satisfies the
15 above-mentioned physicochemical requirements as far as possible.

Detailed Description of the Invention

Surprisingly, it has been found that the problem outlined above is solved by the salt 3-Z-
20 [1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate of formula I.

The monoethanesulphonate according to the invention is characterised by good crystallinity and low amorphisation during grinding and compression. In addition it is not
25 hygroscopic and is readily soluble in physiologically acceptable solvents.

The crystalline form of the monoethanesulphonate of the compound 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone according to the invention is characterised by a melting
30 point of $T_{m.p.} = 305 \pm 5^{\circ}\text{C}$ (determined by DSC = Differential Scanning Calorimetry; evaluated by the peak maximum; heating rate: $10^{\circ}\text{C}/\text{min}$). The value given was determined using a DSC 821[®] made by Messrs Mettler Toledo.

Therefore a first object of the present invention is the salt 3-Z-[1-(4-(N-((4-methyl-

piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate, preferably in crystalline form, characterised by a melting point of $T_{m.p.} = 305 \pm 5^{\circ}\text{C}$ (determined by DSC; evaluation by peak maximum; heating rate: $10^{\circ}\text{C}/\text{min}$).

5

The crystalline form of 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate according to the invention was investigated in more detail by x-ray powder diffraction. The diagram obtained is shown in Figure 1.

10

Table 1 that follows contains the data obtained in this analysis:

Table 1: X-ray powder reflections and intensities (standardised) of 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate.

15

h	k	l	2θ [$^{\circ}$]	d_{hkl} Value [$\text{\AA}$]	Intensity [%]
0	0	1	7.70	11.47	17.7
0	-1	0	8.78	10.07	19.2
-1	0	1	9.47	9.33	26.4
1	0	1	9.82	9.00	32.2
2	0	0	11.59	7.63	30.9
0	-2	1	11.93	7.41	26.3
1	2	0	13.15	6.73	29.6
-2	0	1	13.69	6.47	31.8
2	1	0	14.17	6.24	30.9
3	-1	0	16.32	5.43	41.7
0	1	2	16.72	5.30	29.0

h	k	l	2 θ [$^{\circ}$]	d_{hkl} Value [Å]	Intensity [%]
-1	1	2	16.92	5.238	9.8
3	0	0	17.43	5.08	42.7
2	2	0	17.77	4.99	26.9
1	-4	0	18.58	4.77	31.1
-3	0	1	18.81	4.71	41.8
-2	0	2	19.03	4.66	39.2
3	-3	1	19.73	4.50	40.2
0	4	0	19.87	4.47	6.2
2	-4	1	20.03	4.43	100.0
0	-4	1	20.61	4.31	8.3
-3	-1	1	20.83	4.26	5.5
1	2	2	21.26	4.18	31.1
-1	3	2	21.76	4.08	19.8
0	4	1	22.05	4.03	32.4
3	-4	1	22.19	4.00	10.1
0	3	2	22.57	3.94	25.6
-3	4	1	23.10	3.85	32.3
-1	0	3	23.81	3.73	32.0
1	4	1	24.69	3.60	26.6
1	3	2	24.78	3.58	24.6
0	5	0	24.91	3.572	15.6
-1	5	1	25.42	3.50	23.7
-4	4	1	26.24	3.39	24.8

h	k	l	2 Θ [°]	d _{hkl} Value [Å]	Intensity [%]
3	-2	2	26.91	3.31	22.9
-3	4	2	27.19	3.28	23.9
1	5	0	27.61	3.23	22.0
-1	-5	1	27.95	3.19	22.3
3	-1	3	28.71	3.11	22.1
5	0	0	29.25	3.05	20.2

In Table 1 above the value "2 Θ [°]" denotes the angle of diffraction in degrees and the value "d_{hkl} [Å]" denotes the specified distances in Å between the lattice planes.

- 5 The x-ray powder diagram was recorded, within the scope of the present invention, using a Bruker D8 Advanced-diffractometer fitted with a location-sensitive detector (OED) and a Cu anode as the x-ray source (CuK α radiation, λ = 1.54056 Å, 40 kV, 40 mA).
- 10 According to the findings shown in Table 1 the present invention relates to crystalline 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate, characterised in that in the x-ray powder diagram it has, *inter alia*, the characteristic values d = 5.43 Å, 5.08 Å, 4.71 Å, 4.50 Å and 4.43 Å with an intensity of more than
- 15 40%.

Evaluation of the x-ray powder data obtained yields the unit cell of the compound according to the invention, the crystallographic data of which are provided in Table 2 below:

Formula	C ₂₈ H ₇₈ N ₁₀ O ₁₅ S ₂
Molecular weight	1315.52
Crystal system	triclinic
a	16.332 Å
b	19.199 Å
c	11.503 Å
α	95.27°
β	90.13°
γ	110.83°
V	3354.4 Å ³

5 The unit cell is defined by the lengths of the side of this cell a, b and c, by the relative angles α, β and γ of the cell sides to one another and by the cell volume V (see Table 2). Methods of recording and evaluating x-ray powder diagrams for determining unit cells and their dimensions are known in the prior art and are recognised for characterising the crystalline nature and structure of a product.

10 Thus, the present invention also relates to the crystalline 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate according to the invention, characterised by a unit cell determined by x-ray powder diffractometric measurements, having the following dimensions:

15

a = 16.332 Å

b = 19.199 Å

c = 11.503 Å

α = 95.27°

20

β = 90.13°

25

$\gamma = 110.83^\circ$
 $V = 3354.4 \text{ \AA}^3$

Using a monocrystal it was also possible to determine the space group of the compound according to the invention. The corresponding data are shown in Table 3 below:

Structural resolution	From monocrystal data
Space group	$P\bar{1}$ (#2)
Density (calculated)	2.605 g/ cm ³
Cell contents	> 2 molecules of different conformation > 2 x EtSO₄ > 1 x H₂O

Under standard conditions the monoethanesulphonate of the compound 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone according to the invention is present in the form of the hemihydrate, from which water escapes at a temperature of about 130°C. Figure 2 shows the thermoanalysis.

The present invention also relates to the metabolites of the compound 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate of formula I, to prodrugs of this compound or of these metabolites obtained via, for example, chemical or non-chemical derivatization of the entire molecule or of one or more chemical groups on the molecule, and to the use thereof in a pharmaceutical composition.

Hence, metabolites of the compound 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate may occur via, for example, de-esterification of an ester group on the molecule. This de-esterification may occur in-vivo through the action of specific or a-specific esterases present in the body of the patient to which the drug is

administered.

Prodrugs of the compound 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methoxycarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-

5 monoethanesulphonate or of metabolites thereof may be obtained via, for example, any chemical substitution of a carboxy or amino group present on the molecule or by substitution of the the N-1-atom of the indolinone moiety by a group which may be cleaved *in vivo*.

10 By a group which may be cleaved *in vivo* and converted *in-vivo* into a carboxy group is meant for example a hydroxymethyl group, a carboxy group esterified with an alcohol wherein the alcoholic moiety preferably denotes a C₁₋₆-alkanol, a phenyl-C₁₋₃-alkanol, a C₃₋₆-cycloalkanol, while a C₅₋₈-cycloalkanol may additionally be substituted by one or two C₁₋₃-alkyl groups, a C₅₋₈-cycloalkanol, wherein a methylene group is replaced in the
15 3 or 4 position by an oxygen atom or by an imino group optionally substituted by a C₁₋₃-alkyl, phenyl-C₁₋₃-alkyl, phenyl-C₁₋₃-alkoxy-carbonyl or C₁₋₆-alkyl-carbonyl group and the cycloalkanol moiety may additionally be substituted by one or two C₁₋₃-alkyl groups, a C₄₋₇-cycloalkenol, a C₃₋₅-alkenol, a phenyl-C₃₋₅-alkenol, a C₃₋₅-alkynol or phenyl-C₃₋₅-alkynol, with the proviso that no bond to the oxygen atom starts from a
20 carbon atom which carries a double or triple bond, a C₃₋₆-cycloalkyl-C₁₋₃-alkanol, a bicycloalkanol with a total of 8 to 10 carbon atoms which may additionally be substituted in the bicycloalkyl moiety by one or two C₁₋₃-alkyl groups, a 1,3-dihydro-3-oxo-1-isobenzofuranol or an alcohol of formula

25
$$R_a\text{-CO-O-(R}_b\text{CR}_c\text{)-OH,}$$

wherein

R_a denotes a C₁₋₆-alkyl, C₅₋₇-cycloalkyl, phenyl or phenyl-C₁₋₃-alkyl group,

30 R_b denotes a hydrogen atom, a C₁₋₃-alkyl, C₅₋₇-cycloalkyl or phenyl group and

R_c denotes a hydrogen atom or a C₁₋₃-alkyl group,

and by a group which may be cleaved *in vivo* from an amino group or from the N-1 atom

of the indolinone moiety is meant for example a hydroxy group, an acyl group such as the benzoyl or pyridinoyl group or a C₁₋₁₆-alkyl-carbonyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, an allyloxycarbonyl group, a C₁₋₁₆-alkoxy-carbonyl group such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl or hexadecyloxycarbonyl group, a phenyl-C₁₋₆-alkoxy-carbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a C₁₋₃-alkylsulphonyl-C₁₋₄-alkoxy-carbonyl, C₁₋₃-alkoxy-C₂₋₄-alkoxy-C₂₋₄-alkoxy-carbonyl or R_aCO-O-(R_bCR_c)-O-CO-group wherein

R_a denotes a C₁₋₈-alkyl, C₅₋₇-cycloalkyl, phenyl or phenyl-C₁₋₃-alkyl group,

R_b denotes a hydrogen atom, a C₁₋₃-alkyl, C₅₋₇-cycloalkyl or phenyl group and

R_c denotes a hydrogen atom, a C₁₋₃-alkyl or R_aCO-O-(R_bCR_c)-O-group wherein R_a to R_c are as hereinbefore defined,

and additionally the phthalimido group, while the abovementioned ester groups may also be used as a group which can be converted *in vivo* into a carboxy group.

Preferred prodrug groups for a carboxy group include a C₁₋₆-alkoxy-carbonyl group such as the methoxycarbonyl, ethoxycarbonyl, n-propyloxycarbonyl, isopropyloxycarbonyl, n-butyloxycarbonyl, n-pentyloxycarbonyl, n-hexyloxycarbonyl or cyclohexyloxycarbonyl group or phenyl-C₁₋₃-alkoxy-carbonyl group such as the benzyloxycarbonyl group and

for an amino group or the N-1 group of the indolinone moiety a C₁₋₆-alkoxy-carbonyl group such as the methoxycarbonyl, ethoxycarbonyl, n-propyloxycarbonyl, isopropyloxycarbonyl, n-butyloxycarbonyl, n-pentyloxycarbonyl, n-hexyloxycarbonyl, cyclohexyloxycarbonyl, n-heptyloxycarbonyl, n-octyloxycarbonyl or n-nonyloxycarbonyl group, a phenyl-C₁₋₃-alkoxy-carbonyl group such as the benzyloxycarbonyl group, a phenylcarbonyl group optionally substituted by a C₁₋₃-alkyl group such as the benzoyl or 4-ethyl-benzoyl group, a pyridinoyl group such as the nicotinoyl group, a C₁₋₃-alkylsulphonyl-n-C₂₋₃-alkoxy-carbonyl or C₁₋₃-alkoxy-C₂₋₃-alkoxy-C₁₋₄-alkoxy-carbonyl

group such as the 2-methylsulphonylethoxycarbonyl or 2-(2-ethoxy)-ethoxycarbonyl group.

Moreover, the saturated alkyl and alkoxy moieties containing more than 2 carbon atoms mentioned in the definitions above as well as the alkanoyl and unsaturated alkyl moieties which contain more than 3 carbon atoms also include the branched isomers thereof such as the isopropyl, tert.butyl, isobutyl group, etc.

For the chemical synthesis of the above-mentioned metabolites and prodrugs, reference is made to WO 01/27081.

Experimental studies have shown that a metabolite of the compound 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylocarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate is the de-esterified 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone. The in-vitro inhibitory activity of this metabolite on several kinases has been evaluated, using standard known kinase inhibition assays as well as a standard known cellular proliferation inhibition assay (inhibition of the proliferation of Human Umbilical Cord Endothelial Cells stimulated by the VEGF, the so-called "HUVEC cellular assay"). These experimental results have shown that this metabolite inhibits several kinases, such as VEGFR-2, VEGFR-3, Her-2, FGFR-1, PDGFR-alpha or InsR, as well as the proliferation of HUVEC VEGF stimulated cells.

Furthermore, the compounds in accordance with the present invention may be administered to a patient in need thereof in any type of galenical form such as tablets, capsules or in a liquid formulation.

An especially suitable pharmaceutical formulation for the compounds in accordance with the present invention is soft gelatine capsules. Suitable soft gelatine capsules for the encapsulation of pharmaceutical compounds and the process for their preparation are described, for example, in GB patent No. 395546, US patent No. 2,720,463, US patent No. 2,870,062, US patent No. 4,829,057, and in the following publications: ANON (Verpack-Rundsch., Vol. 21, No. 1, Jan 1970, pp. 136-138), Lachman et al. (The Theory and Practice of Industrial Pharmacy, Chap. 13, published by Lea & Febiger,

1970), Ebert (Soft Gelatine Capsules: A Unique Dosage Form, reprint from Pharmaceutical Technology, Oct. 1977) and R. F. Jimerson (Soft Gelatine Capsule Update, Drug Development and Industrial Pharmacy, Vol. 12 (8 & 9), pp. 1133-1144, 1986).

5

Experimental section

The HPLC data given below were measured using the parameters listed hereinafter:

- 10 Column: Inertsil ODS-2, 5 μ m, 53 x 4.0 mm; solvent A: 0.2% aqueous KH_2PO_4 solution, adjusted to pH = 6.0 with dilute sodium hydroxide solution; solvent B: acetonitrile; column temperature: 45°C; flow: 1mL/min; gradient system: within 5 minutes, from 5% to 30% solvent B, then maintained for 1 minute at 30% solvent B and then within 9 minutes increased to 55% solvent B, then maintained for 4 minutes at 55% B;
- 15 concentration of the sample solution: 5 mg/mL in acetonitrile/water = 3 : 7; injection volume: 3 μ L; detection at 225 nm and 210 nm, respectively.

Example 1

3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

5

10.5 g (30.0 mmol) of 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone (for preparation see WO 01/27081 mentioned above) and 8.60 g (33.0 mmol) N-[(4-methyl-piperazin-1-yl)-methylcarbonyl]-N-methyl-*p*-phenylenediamine (for preparation see WO 01/27081 mentioned above) are dissolved in 80 mL of dimethylformamide and stirred for 1 hour at 80°C. After cooling 6.50 mL of piperidine are added and the mixture is stirred for another two hours at ambient temperature. Water is added, the precipitate formed is suction filtered and washed with a little water. The residue is suspended in 200 mL of methanol, suction filtered and washed with cold water and diethyl ether. The substance is dried *in vacuo* at 110 °C.

15

Yield:	12.4 g (77% of theory),			
IR spectrum:	1610, 1655, 1711 cm ⁻¹			
T _{m.p.} =	253°C			
Empirical formula:	C ₃₁ H ₃₃ N ₅ O ₄			
ESI mass spectrum:	m/z = 540 [M+H] ⁺			
Elemental analysis:	calculated:	C 68.99	H 6.16	N 12.98
	found:	C 68.32	H 6.29	N 12.85

20

Example 2

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3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate

30

605 g (1.12 mol) of 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone are suspended in 9 litres of methanol and heated to 50°C. 183.7 g (1.121 mol) of 70% aqueous ethanesulphonic acid are added. The solution obtained is cooled to 40°C and 4.5 litres of *tert.*-butylmethylether are added. After a few minutes crystallisation sets in. To achieve total precipitation the mixture is stirred for another 16 hours at ambient

temperature. After cooling to 10°C it is suction filtered, washed with 2 litres of *tert.*-butylmethylether and dried at 40°C *in vacuo*.

Yield: 638 g (87.6% of theory)

5 $T_{m.p.} = 305 \pm 5^{\circ}\text{C}$ (DSC 10K/min)

Purity according to HPLC: 99.4%

Water content: 1.0 to 2.0% (KF)

10 Brief description of the Figures

Figure 1 shows the X-ray powder diffractogram of crystalline 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate.

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Figure 2 shows the thermoanalysis and determination of the melting point (DSC) of crystalline 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate.

Patent Claims

- 5 1. 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate.
2. 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate
- 10 according to claim 1 in crystalline form, characterised by a melting point of $T_{m.p.} = 305 \pm 5^{\circ}\text{C}$ (determined by DSC; evaluation using peak-maximum; heating rate: $10^{\circ}\text{C}/\text{min}$).
3. Crystalline 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-
- 15 monoethanesulphonate according to claim 2, characterised in that in the X-ray powder diagram it shows, *inter alia*, the characteristic values $d = 5.43 \text{ \AA}$, $5.08 \text{ \AA}$, $4.71 \text{ \AA}$, $4.50 \text{ \AA}$ and $4.43 \text{ \AA}$ with an intensity of more than 40%.
4. Crystalline 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-
- 20 amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate according to claim 2, characterised by a unit cell determined by X-ray powder diffractometric measurements having the following dimensions:
- a = 16.332 $\text{\AA}$,
- 25 b = 19.199 $\text{\AA}$,
- c = 11.503 $\text{\AA}$,
- $\alpha = 95.27^{\circ}$,
- $\beta = 90.13^{\circ}$,
- $\gamma = 110.83^{\circ}$ and
- 30 V = 3354.4 $\text{\AA}^3$
5. Crystalline 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate according to one of claims 2 to 4, characterised in that it is in

the form of the hemihydrate.

6. Pharmaceutical composition containing the salt 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate according to one of claims 1 to 5 optionally together with one or more inert carrier and/or diluents.
7. A metabolite of the salt 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate.
8. A prodrug of the salt 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate according to one of claims 1 to 5 or of a metabolite according to claim 7.
9. Pharmaceutical composition containing a metabolite according to claim 7 or a prodrug according to claim 8, optionally together with one or more inert carrier and/or diluents.
10. Use of 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate according to one of claims 1 to 5 for preparing a pharmaceutical composition which is suitable for treating excessive or abnormal cell proliferation.
11. Use of a metabolite according to claim 7 or a prodrug according to claim 8 for preparing a pharmaceutical composition which is suitable for treating excessive or abnormal cell proliferation.
12. Process for preparing a pharmaceutical composition according to claim 6, characterised in that the salt 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate according to one of claims 1 to 5 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

13. Process for preparing a pharmaceutical composition according to claim 6, characterised in that a metabolite according to claim 7 or a prodrug according to claim 8 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

Abstract

5 The present invention relates to the compound 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate of formula I and the use thereof as a pharmaceutical composition.

10 Formula I:

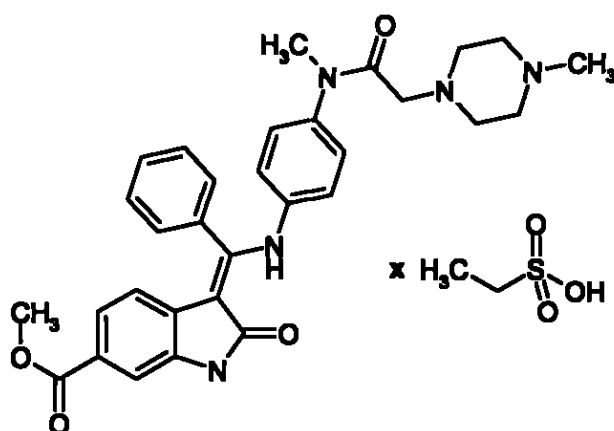


Figure 1: X-ray powder diffractogram of crystalline 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate.

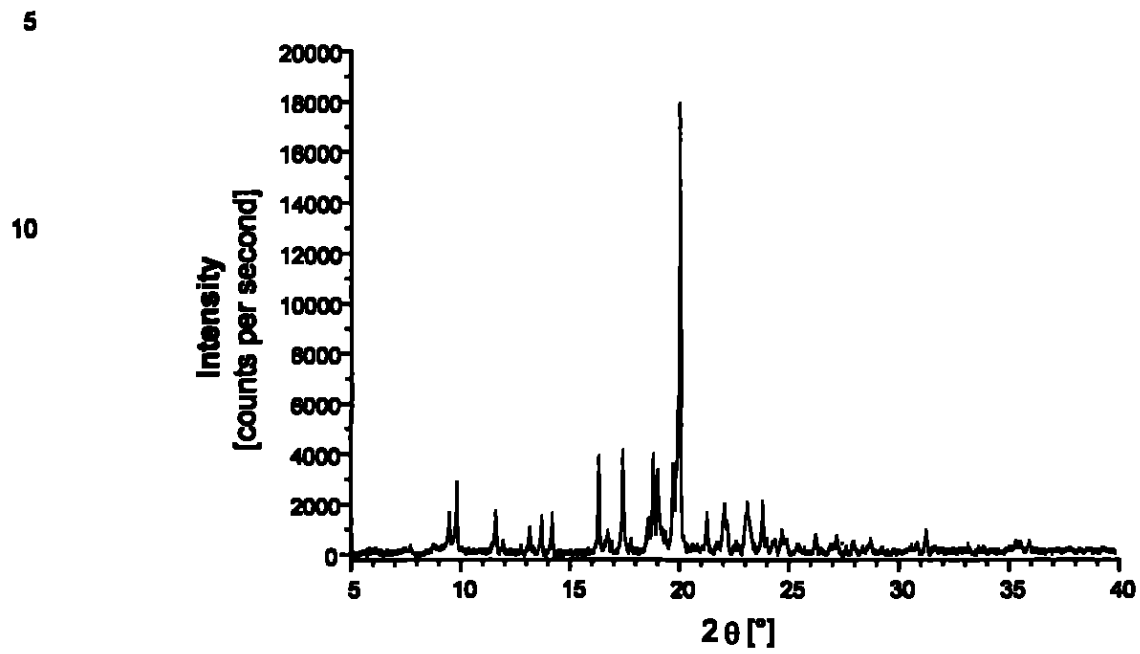
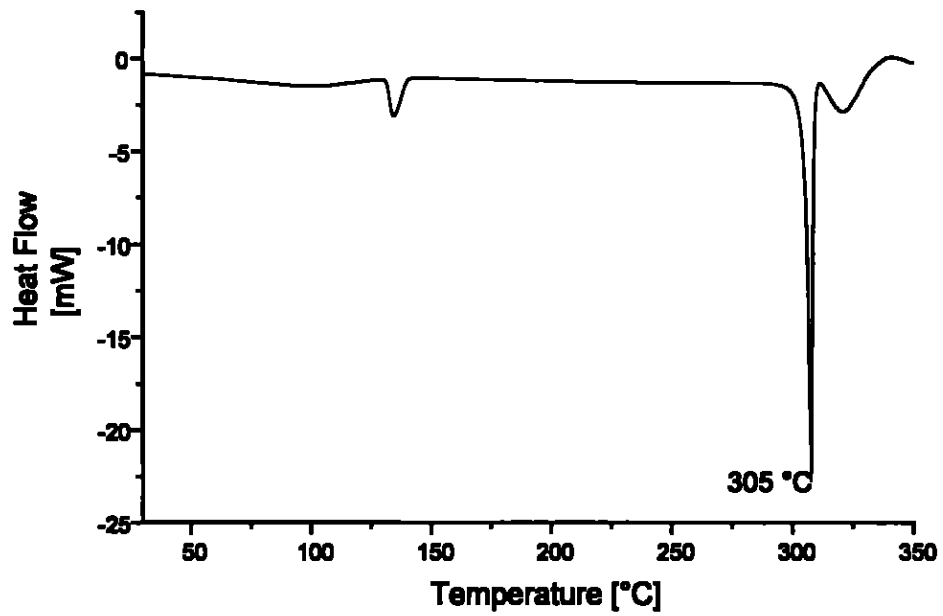


Figure 2: Thermoanalysis and determination of the melting point (DSC) of crystalline 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate.

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To: BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG DE-55216 Ingelheim am Rhein GERMANY		Eingang CD Patents 05. Okt. 2003 SR gesehen erledigt GO EC	NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION (PCT Rule 48.1) EINGEGANGEN 07. Okt. 2003
		Date of mailing (day/month/year) 08/10/2003	
Applicant's or agent's file reference Case 1/1374		FOR FURTHER ACTION See paragraphs 1 and 4 below	
International application No. PCT/EP 03/07822		International filing date (day/month/year) 18/07/2003	
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG		ZA Patente Frist: 8.12.2003 Termin not: 8.10.05	

B. St.
 Termin
 Streichen
 Keine
 Änderungen
 Kasten
 10.1.

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

Filing of amendments and statement under Article 19:
 The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 48):

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

Where? Directly to the International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland
 Facsimile No.: (41-22) 740.14.35

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

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

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

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

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

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

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

Within 18 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 18 months from the priority date or could not be elected because they are not bound by Chapter II.

cc B. St. 7
 GO-6
 1/15
 1.10.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 661 epo nl, Fax: (+31-70) 340-3018	Authorized officer Panayota Georgakopoulou
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PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference Case 1/1374	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 03/07822	International filing date (day/month/year) 18/07/2003	(Earliest) Priority Date (day/month/year) 24/07/2002
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG		

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

This International Search Report consists of a total of 05 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

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

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

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

☐ contained in the international application in written form.

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

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

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

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

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

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

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 36.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

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

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/07822

30

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/34 A61K31/404 A61P35/04

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

EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 27081 A (HILBERG FRANK ; SPEVAK WALTER (AT); MEEL JACOBUS VAN (AT); TONTSCH) 19 April 2001 (2001-04-19) cited in the application example 473	1-6, 9, 10, 12, 13
Y	WO 01 27080 A (SPEVAK WALTER ; MEEL VAN JACOBUS (AT); TONTSCH GRUNT ULRIKE (AT); B) 19 April 2001 (2001-04-19) claims; examples	1-6, 9, 10, 12, 13
P, Y	WO 02 081445 A (HILBERG FRANK ; VAN MEEL JACOBUS (AT); BOEHRINGER INGELHEIM PHARMA) 17 October 2002 (2002-10-17) claims; examples	1-6, 9, 10, 12, 13



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

30 September 2003

Date of mailing of the international search report

08/10/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patenthuis 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-3040, Tx. 31 051 epo nl
Fax: (+31-70) 340-3010

Authorized officer

Menegaki, F

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

Claims Nos.: 7,8,11

Present claims 7,8,11 relate to an extremely large number of possible prodrugs and/or metabolites. In fact, the claims contain so many options that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely Claims 1-6,9,10,12,13.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/07822

42

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 7,8,11
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/07822

43

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0127081	A	19-04-2001	DE 19949208 A1	19-04-2001
			DE 10042696 A1	14-03-2002
			AU 1023301 A	23-04-2001
			BG 106587 A	31-01-2003
			BR 0014735 A	16-07-2002
			CA 2387013 A1	19-04-2001
			CN 1391557 T	15-01-2003
			CZ 20021410 A3	17-07-2002
			EE 200200197 A	16-06-2003
			WO 0127081 A1	19-04-2001
			EP 1224170 A1	24-07-2002
			HU 0204587 A2	28-05-2003
			JP 2003511441 T	25-03-2003
			NO 20021719 A	11-04-2002
			SK 6462002 A3	06-08-2002
WO 0127080	A	19-04-2001	DE 19949209 A1	19-04-2001
			AU 7663100 A	23-04-2001
			WO 0127080 A2	19-04-2001
			EP 1224169 A2	24-07-2002
WO 02081445	A	17-10-2002	DE 10117204 A1	10-10-2002
			WO 02081445 A1	17-10-2002
			US 2003092756 A1	15-05-2003

PCT

REQUEST

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

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) Case 1/1374

Box No. I TITLE OF INVENTION

3-Z-[1-(4-(N-(4-Methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-8-methoxycarbonyl-2-indolinone-monoethanesulphonate and the use thereof as a pharmaceutical composition

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Boehringer Ingelheim
Pharma GmbH & Co. KG

55218 Ingelheim/Rhein
DE

Telephone No.
07351-54-4390

Facsimile No.
07351-54-4377

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:
DE

State (that is, country) of residence:
DE

This person is applicant for the purposes of:

☐ all designated States

☒ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

ROTH, Gerald Jürgen
Akazienweg 47
88400 Biberach
DE

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (if this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
DE

State (that is, country) of residence:
DE

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

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

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☐ agent

☐ common representative

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

Telephone No.

Facsimile No.

Teleprinter No.

Agent's registration No. with the Office

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

See Notes to the request form

Box No. V DESIGNATION OF STATES

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

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

Regional Patent

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

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

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

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

☐ ☐ ☐

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

Box No. VI PRIORITY CLAIM				
The priority of the following earlier application(s) is hereby claimed:				
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 24. Juli 2002 (24.07.2002)	102 33 500.1	DE		
item (2)				
item (3)				
item (4)				
item (5)				
☐ Further priority claims are indicated in the Supplemental Box.				
The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:				
☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box				
* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(II)):				
Box No. VII INTERNATIONAL SEARCHING AUTHORITY				
Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):				
ISA / EP				
Request to use results of earlier search; reference to that search (If an earlier search has been carried out by or requested from the International Searching Authority):				
Date (day/month/year)	Number	Country (or regional Office)		
Box No. VIII DECLARATIONS				
The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):				Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor			:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent			:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application			:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)			:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty			:

Box No. IX CHECK LIST; LANGUAGE OF FILING																																																							
This international application contains: (a) In paper form, the following number of sheets: <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">request (including declaration sheets) :</td> <td style="width: 20%; text-align: right;">5</td> </tr> <tr> <td>description (excluding sequence listings and/or tables related thereto) :</td> <td style="text-align: right;">14</td> </tr> <tr> <td>claims :</td> <td style="text-align: right;">3</td> </tr> <tr> <td>abstract :</td> <td style="text-align: right;">1</td> </tr> <tr> <td>drawings :</td> <td style="text-align: right;">2</td> </tr> <tr> <td>Sub-total number of sheets :</td> <td style="text-align: right;">25</td> </tr> <tr> <td>sequence listings :</td> <td></td> </tr> <tr> <td>tables related thereto :</td> <td></td> </tr> <tr> <td colspan="2"><i>(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)</i></td> </tr> <tr> <td>Total number of sheets :</td> <td style="text-align: right;">25</td> </tr> </table> (b) ☐ only in computer readable form (Section 801(a)(i)) (i) ☐ sequence listings (ii) ☐ tables related thereto (c) ☐ also in computer readable form (Section 801(a)(ii)) (i) ☐ sequence listings (ii) ☐ tables related thereto Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the ☐ sequence listings: ☐ tables related thereto: <i>(additional copies to be indicated under items 9(II) and/or 10(II), in right column)</i>	request (including declaration sheets) :	5	description (excluding sequence listings and/or tables related thereto) :	14	claims :	3	abstract :	1	drawings :	2	Sub-total number of sheets :	25	sequence listings :		tables related thereto :		<i>(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)</i>		Total number of sheets :	25	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item): <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">1. ☒ fee calculation sheet</td> <td style="width: 20%; text-align: right;">1</td> </tr> <tr> <td>2. ☒ original separate power of attorney</td> <td style="text-align: right;">2</td> </tr> <tr> <td>3. ☐ original general power of attorney</td> <td></td> </tr> <tr> <td>4. ☐ copy of general power of attorney; reference number, if any:</td> <td></td> </tr> <tr> <td>5. ☐ statement explaining lack of signature</td> <td></td> </tr> <tr> <td>6. ☒ priority document(s) identified in Box No. VI as item(s):</td> <td style="text-align: right;">1</td> </tr> <tr> <td>7. ☐ translation of international application into (language):</td> <td></td> </tr> <tr> <td>8. ☐ separate indications concerning deposited microorganism or other biological material</td> <td></td> </tr> <tr> <td>9. ☐ sequence listings in computer readable form (indicate type and number of carriers)</td> <td></td> </tr> <tr> <td style="margin-left: 20px;">(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :</td> <td></td> </tr> <tr> <td style="margin-left: 20px;">(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :</td> <td></td> </tr> <tr> <td style="margin-left: 20px;">(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listings mentioned in left column :</td> <td></td> </tr> <tr> <td>10. ☐ tables in computer readable form related to sequence listings (indicate type and number of carriers)</td> <td></td> </tr> <tr> <td style="margin-left: 20px;">(i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application) :</td> <td></td> </tr> <tr> <td style="margin-left: 20px;">(ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater) :</td> <td></td> </tr> <tr> <td style="margin-left: 20px;">(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :</td> <td></td> </tr> <tr> <td>11. ☐ other (specify):</td> <td></td> </tr> </table>	1. ☒ fee calculation sheet	1	2. ☒ original separate power of attorney	2	3. ☐ original general power of attorney		4. ☐ copy of general power of attorney; reference number, if any:		5. ☐ statement explaining lack of signature		6. ☒ priority document(s) identified in Box No. VI as item(s):	1	7. ☐ translation of international application into (language):		8. ☐ separate indications concerning deposited microorganism or other biological material		9. ☐ sequence listings in computer readable form (indicate type and number of carriers)		(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :		(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listings mentioned in left column :		10. ☐ tables in computer readable form related to sequence listings (indicate type and number of carriers)		(i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application) :		(ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater) :		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :		11. ☐ other (specify):	
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(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :																																																							
11. ☐ other (specify):																																																							
Figure of the drawings which should accompany the abstract: 1	Language of filing of the international application: deutsch																																																						

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

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

Boehringer Ingelheim Pharma GmbH & Co. KG ppa. Dr. Rothmeyer	I.A. Dr. Obracht
--	---------------------------------

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY
Eingang CO Patents

29

- 1. Okt. 2003 From the INTERNATIONAL BUREAU

PCT

To:

SB

gesehen

erledigt

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

BOEHRINGER INGELHEIM PHARMA GMBH &
CO. KG
55216 Ingelheim/Rhein
Germany

Date of mailing (day/month/year) 18 September 2003 (18.09.03)	
Applicant's or agent's file reference Case 1/1374	IMPORTANT NOTIFICATION
International application No. PCT/EP03/07822	International filing date (day/month/year) 18 July 2003 (18.07.03)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 24 July 2002 (24.07.02)
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
24 July 2002 (24.07.02)	102 33 500.1	DE	19 Augu 2003 (19.08.03)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.88.75	Authorized officer Mathieu BLANC (Fax 338 89 75) Telephone No. (41-22) 338 8988
--	---

PATENT COOPERATION TREATY

11. Dez. 2003

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NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

EINGEGANGEN
15. Dez. 2003
Erledigt

To:

BOEHRINGER INGELHEIM PHARMA GMBH &
CO. KG
55216 Ingelheim/Rhein
Germany

Date of mailing (day/month/year) 03 December 2003 (03.12.03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference Case 1/1374	
International application No. PCT/EP03/07822	International filing date (day/month/year) 18 July 2003 (18.07.03)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality DE	State of Residence DK
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The international Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address BOCK, Thomas Soeren Norbys Allee 5-1 DK-2300 Kopenhagen Denmark	State of Nationality DE	State of Residence DK
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

The person identified in Box 2 should be added to the record as applicant/inventor for the purpose of the United States of America only.

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.89.75	Authorized officer Rosana REYES (Fax : 338 89 75) Telephone No. (41-22) 338 8471
--	--

Eingang CD Patents

11. Dez. 2003

PATENT COOPERATION TREATY

EINGEGANGEN

15. Dez. 2003

Erled.

From the INTERNATIONAL BUREAU

To:

BOEHRINGER INGELHEIM PHARMA GMBH &
CO. KG
55216 Ingelheim/Rhein
Germany

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year)

03 December 2003 (03.12.03)

Applicant's or agent's file reference

Case 1/1374

International application No.

PCT/EP03/07822

International filing date (day/month/year)

18 July 2003 (18.07.03)

IMPORTANT NOTIFICATION

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

State of Nationality

DE

State of Residence

AT

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

HILBERG, Frank
Pilgramgasse 18/22
A-1050 Wien
Austria

State of Nationality

DE

State of Residence

AT

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

The person identified in Box 2 should be added to the record as applicant/inventor for the purpose of the United States of America only.

4. A copy of this notification has been sent to:

☐ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338 89 76

Authorized officer

Rosana REYES (Fax : 338 89 75)

Telephone No. (41-22) 338 8471

From the INTERNATIONAL BUREAU

PCTNOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
55218 Ingelheim/Rhein
ALLEMAGNE

Eingang CD Patents

23 Feb. 2004

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EINGEGANGEN

23. Feb. 2004

Erled

IMPORTANT NOTICE

Date of mailing (day/month/year)

12 February 2004 (12.02.2004)

Applicant's or agent's file reference

Case 1/1374

International application No.

PCT/EP2003/007822

International filing date (day/month/year)

18 July 2003 (18.07.2003)

Priority date (day/month/year)

24 July 2002 (24.07.2002)

Applicant

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

AU, AZ, BY, CH, CN, CO, DE, DZ, EP, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DK, DM, EA, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-h)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 12 February 2004 (12.02.2004) under No. WO 2004/013099

ERFASST
SG

4. **TIME LIMITS** for filing a demand for international preliminary examination and for entry into the national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Gijsbertus Beijer - Carlos Roy

Facsimile No.(41-22) 740.14.35

Telephone No.(41-22) 338.91.11

Eingang CD Patents

30. April 2004

PATENT COOPERATION TREATY

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From the INTERNATIONAL BUREAU

To:

BOEHRINGER INGELHEIM PHARMA GMBH &
CO. KG
55216 Ingelheim/Rhein
Germany

EINGEGANGEN

04. Mai 2004

Erled

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

Date of mailing (day/month/year) 16 April 2004 (16.04.2004)		
Applicant's or agent's file reference Case 1/1374		
IMPORTANT INFORMATION		
International application No. PCT/EP2003/007822	International filing date (day/month/year) 18 July 2003 (18.07.2003)	Priority date (day/month/year) 24 July 2002 (24.07.2002)
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al		

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,
SI, SK, TR

National : BG, CA, CN, DE, GB, IL, JP, KP, KR, MN, NO, PL, RO, RU, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, CZ, DK, DM, DZ, EC,
EE, ES, FI, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MW, MX, MZ, NI, NZ, OM, PH, PT, SC, SD, SE, SG, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ,
VC, VN, YU, ZA, ZM, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 38(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 38(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer: Suaton, Sophie
Facsimile No. (41-22) 338.89.75	Telephone No. (41-22) 338 1

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

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only		
Identification of IPEA		Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference
International application No. PCT/EP 03/07822	International filing date (day/month/year) 18 July 2003 (18/07/03)	(Earliest) Priority date (day/month/year) 24 July 2002 (24/07/02)
Title of invention 3-Z-[1-(4-(N-((4-Methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate and the use thereof as a pharmaceutical composition		
Box No. II APPLICANT(S)		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Boehringer Ingelheim Pharma GmbH & Co. KG 55216 Ingelheim/Rhein De		Telephone No. 07351-54-4390
		Facsimile No. 07351-54-4377
		Teleprinter No.
		Applicant's registration No. with the Office
State (that is, country) of nationality: DE		State (that is, country) of residence: DE
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ROTH, Gerald Jürgen Akazienweg 47 88400 Biberach DE		
State (that is, country) of nationality: DE		State (that is, country) of residence: DE
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) SIEGER, Peter Wielandstrasse 27 88441 Mittelhörsach DE		
State (that is, country) of nationality: DE		State (that is, country) of residence: DE
☒ Further applicants are indicated on a continuation sheet.		

Continuation of Box No. II APPLICANT(S)

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

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

LINZ, Guenter
Eschenweg 8
88441 Mittelhilberach
DEState (that is, country) of nationality:
DEState (that is, country) of residence:
DE

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

RALL, Werner
Beethovenstr. 33
88441 Mittelhilberach
DEState (that is, country) of nationality:
DEState (that is, country) of residence:
DE

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

State (that is, country) of nationality:

State (that is, country) of residence:

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

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☐ agent ☐ common representativeand ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family names followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)*

Telephone No.

Facsimile No.

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

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

☒ the international application as originally filedthe description ☒ as originally filed☐ as amended under Article 34the claims ☒ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☒ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 69.1(d).4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a).

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

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Box No. VI CHECK LIST

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

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

For International Preliminary Examining Authority use only

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

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

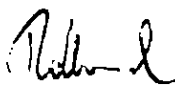
- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to a sequence listing |
| 4. ☐ copy of general power of attorney; reference number, if any: | 8. ☐ other (specify): |

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

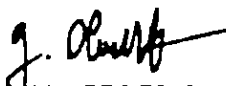
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Boehringer Ingelheim Pharma GmbH & Co. KG

ppa.



i.A.



Dr. Reinfried ROTHERMEL

Dr. Gauthier OBRECHT

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PATENT COOPERATION TREATY

77 58

EINGEGANGEN
12 Feb. 2004
Erled.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:		BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG DE-55216 Ingelheim am Rhein ALLEMAGNE		Eingang CD Patents 11. Feb. 2004		NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY (PCT Rules 59.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))	
SB		gesehen		erledigt		Date of mailing (day/month/year) 10-02-2004	
20		60					
1-1374				IMPORTANT NOTIFICATION			
International application No. PCT/EP03/07822		International filing date (day/month/year) 18/07/2003		Priority date (day/month/year) 24/07/2002			
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al.							

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

20/01/2004

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is after the expiration of 19 months from the priority date. Consequently, in respect of some Offices, the demand does not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)) and the acts for entry into the national phase must therefore be performed within 20 months from the priority date (or later in some Offices). However, in respect of some other Offices, the time limit of 30 months (or later) may nevertheless apply. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer FERRO VASCONCELOS M Tel. (+49-89) 2399-7905
---	--



PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG DE-55218 Ingelheim am Rhein ALLEMAGNE		Eingang CD Patents 23. Feb. 2004		PCT EINGEGANGEN 24. Feb. 2004	
CD Patents Frist: 20.05.2004 SG Termin not.: 20.03.04		58 gesehen erledigt 60 60 B. & T. S. + W. entfernen - Keine Antwort.		WRITTEN OPINION PCT Rule 66) 60 24.02.04	
Applicant's or agent's file reference ... 701-1374-40		REPLY DUE within 3 month(s) from the above date of mailing			
International application No. PCT/EP 03/07822	International filing date (day/month/year) 18.07.2003	Priority date (day/month/year) 24.07.2002			
International Patent Classification (IPC) or both national classification and IPC C07D209/34					
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al.					

- This written opinion is the first drawn up by this International Preliminary Examining Authority.
- This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application
- The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.8.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
- The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 24.11.2004

Name and mailing address of the international preliminary examining authority:



European Patent Office
D-80288 Munich
Tel. +49 89 2369 - 0 Tlx: 523858 epmu d
Fax: +49 89 2369 - 4485

Authorized Officer

Menegaki, F

Formalities officer (incl. extension of time limits)
Ambroa, J.R.
Telephone No. +49 89 2369-8012



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WRITTEN OPINION

International application No. PCT/EP 03/07822

I. Basis of the opinion

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, Pages

1-14 as originally filed

Claims, Numbers

1-13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
 - ☐ the language of publication of the international application (under Rule 48.3(b)).
 - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority in written form.
 - ☐ furnished subsequently to this Authority in computer readable form.
 - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
4. The amendments have resulted in the cancellation of:
- ☐ the description, pages:
 - ☐ the claims, Nos.:
 - ☐ the drawings, sheets:
5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).
6. Additional observations, if necessary:

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

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

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WRITTEN OPINION

International application No. PCT/EP 03/07822

☐ the entire international application,

☒ claims Nos. 7,8,11

because:

☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-13 YES
Inventive step (IS)	Claims	1-13 NO
Industrial applicability (IA)	Claims	1-8,9,10,12,13 YES

2. Citations and explanations

see separate sheet

(III)

Claims 7,8,11 refer to all possible metabolites and/or prodrugs of the claimed compound salt and therefore they do not fulfill the requirements of Art.6 PCT. Moreover, in view of the fact that said claims are not covered by the Search Report no preliminary examination has been carried out.

(V)

Having regard to the International Search Report the claimed monoethanesulfonate salt was not disclosed in the prior art documents

(D1) WO 01/27081; (D2) WO 01/27080.

(D3) WO 02/081445, a P-document not relevant at this stage, discloses structurally similar 6-substituted indolinone derivatives without mentioning any specific salts thereof.

The requirements of Art.33(2) PCT appear to be fulfilled.

The problem underlying the invention appears to be the provision of the monoethanesulfonate salt of the compound (473) disclosed in prior art document (D1), having improved properties as listed on p.2-3 of the description.

The Applicant has not substantiated any advantage over nearest prior art Ex.473 of (D1). Moreover, although Claims 7,8 and 11 are not covered by the Search Report, it is noted that evidence of an unexpected advantage of the claimed salt, due to its physicochemical properties, would not belong to the same inventive concept of any prodrugs and/or metabolites of the substance itself.

The requirements of Art.33(3) PCT do not appear to be fulfilled.

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:		Eingang CD Patents		NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)	
BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG DE-55216 Ingelheim am Rhein ALLEMAGNE		15. Dez. 2004			
		SB	gesehen	erledigt	
		GO	60		
		Date of mailing (day/month/year) 13.12.2004			
Applicant's or agent's file reference E-3-11/1374			IMPORTANT NOTIFICATION		
International application No. PCT/EP 03/07822	International filing date (day/month/year) 18.07.2003	Priority date (day/month/year) 24.07.2002			
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al.					

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

4. REMINDER

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

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

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

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523856 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Ambroa, J.R. Tel. +49 89 2399-8012	
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference ...	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAA16)	
International application No. PCT/EP 03/07822	International filing date (day/month/year) 18.07.2003	Priority date (day/month/year) 24.07.2002
International Patent Classification (IPC) or both national classification and IPC C07D209/34		
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al.		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 5 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 807 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.		
3. This report contains indications relating to the following items: I ☒ Basis of the opinion II ☐ Priority III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application		
Date of submission of the demand 20.01.2004	Date of completion of this report 13.12.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80288 Munich Tel. +49 89 2399 - 0 Tx: 523858 apmu d Fax: +49 89 2399 - 4485	Authorized Officer Menegaki, F Telephone No. +49 89 2399-8277 	

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP 03/07822

I. Basis of the report

1. With regard to the **elements** of the international application (*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 since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-14 as originally filed

Claims, Numbers

1-13 as originally filed

Drawings, Sheets

1, 2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

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

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP 03/07822

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 7,8,11

because:

☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

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	1-13
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-13
Industrial applicability (IA)	Yes: Claims	1-6,9,10,12,13
	No: Claims	

2. Citations and explanations

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP 03/07822

see separate sheet

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INTERNATIONAL PRELIMINARY

International application No. PCT/EP 03/07822

EXAMINATION REPORT - SEPARATE SHEET

(III)

Claims 7,8,11 refer to all possible metabolites and/or prodrugs of the claimed compound salt and therefore they do not fulfil the requirements of Art.6 PCT. Moreover, in view of the fact that said claims are not covered by the Search Report no preliminary examination has been carried out.

(V)

Having regard to the International Search Report the claimed monoethanesulfonate salt was not disclosed in the prior art documents

(D1) WO 01/27081; (D2) WO 01/27080.

(D3) WO 02/081445, a P-document not relevant at this stage, discloses structurally similar 6-substituted indolinone derivatives without mentioning any specific salts thereof.

The requirements of Art.33(2) PCT appear to be fulfilled.

The problem underlying the invention appears to be the provision of the monoethanesulfonate salt of the compound (473) disclosed in prior art document (D1), having improved properties as listed on p.2-3 of the description.

The Applicant has not substantiated any advantage over nearest prior art Ex.473 of (D1). Moreover, although Claims 7,8 and 11 are not covered by the Search Report, it is noted that evidence of an unexpected advantage of the claimed salt, due to its physicochemical properties, would not belong to the same inventive concept of any prodrugs and/or metabolites of the substance itself.

The requirements of Art.33(3) PCT do not appear to be fulfilled.

Traducción

TRATADO DE COOPERACIÓN DE PATENTES
PCT
INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 y Regla 70 del PCT)

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Referencia del expediente del agente o solicitante	PARA ACTUACIONES ADICIONALES	Ver notificación de Transmisión del Reporte de Examen Preliminar (Formato PCT/IPEA418)
Solicitud Internacional No. PCT/EP03/07822	Fecha de presentación internacional (día/mes/año) 18.07.2003	Fecha de prioridad (día/mes/año) 24.07.2002
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC C07D 209/34		
Solicitante BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al.		

1. Este Informe de examen preliminar internacional ha sido preparado por esta Administración encargada del Examen Preliminar Internacional y se envía al solicitante en concordancia con el artículo 36.
2. Este INFORME consta de una total de 5 hojas, incluyendo la portada
- ☐ Este informe también se acompaña de ANEXOS, esto es documentos de la descripción, reivindicaciones y/o dibujos que han sido corregidos y que son la base de este Informe y/o documentos que contienen rectificaciones realizadas ante esta Administración (Ver Regla 70.18 y Sección 607 de las Instrucciones Administrativas según el PCT)

Estos anexos constan de un total de _____ hojas.

3. Este informe contiene indicaciones relativas a los siguientes aspectos:

- I ☒ Fundamentos del Informe
- II ☐ Prioridad
- III ☒ No se establece concepto relativo a la novedad, nivel inventivo y aplicación Industrial
- IV ☐ Carencia de unidad de la invención
- V ☒ Declaración razonada según el artículo 35(2), en relación con la novedad, nivel inventivo o aplicación Industrial; citaciones y explicaciones que soportan dicha declaración
- VI ☐ Ciertos documentos citados
- VII ☐ Ciertos defectos de la solicitud Internacional
- VIII ☐ Ciertas observaciones respecto a la solicitud Internacional

Fecha de presentación de la demanda 20.01.2004	Fecha de terminación de este reporte 13.12.2004
Nombre y dirección de correo de la autoridad encargada del examen preliminar  Oficina Europea de Patentes D-80298 Munich Tel. +49 89 2369 - 0 Tlx 523656 epmu d Fax: +49 89 2369 - 4465	Funcionario Autorizado Menegaki, F Teléfono No. +49 89 2369-8277

Formato PCT/IPEA/409 (portada) (julio 1998)

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I. Base del Informe

1. Respecto a los elementos de la solicitud internacional: *(Las hojas de reemplazo que han sido entregadas a la Oficina receptora en respuesta a la invitación bajo el Artículo 14 se referirán en este Informe como "originalmente presentadas" y no se anexan a este Informe ya que ellas no contienen modificaciones (Regla 70.16 y 70.17)).*

La descripción, páginas

1-14 como se presentaron originalmente

Las reivindicaciones, números

1-13 como se presentaron originalmente

Los dibujos, hojas

1, 2 como se presentaron originalmente

2. Respecto al lenguaje, todos los elementos marcados anteriormente estuvieron disponibles o fueron enviados a la Administración en el lenguaje en que se presentó la solicitud internacional, a menos que se indique otra cosa en este punto.

Estos elementos estuvieron disponibles o fueron enviados a esta Administración en el siguiente lenguaje _____ el cual es:

- ☐ el lenguaje de la traducción enviada para propósitos de la búsqueda internacional (bajo Regla 23.1 (b)).
☐ el lenguaje de la publicación de la solicitud internacional (bajo Regla 48.3(b)).
☐ el lenguaje de la traducción entregada con propósitos del examen preliminar internacional (bajo Regla 55.2 y/o 55.3).

3. Respecto a cualquier secuencia de nucleótido y/o amino ácidos divulgada en la solicitud internacional, el examen preliminar internacional se llevó a cabo con base en el listado de secuencias:

- ☐ contenido en la solicitud internacional en forma escrita
☐ presentado junto con la solicitud internacional en forma legible por computador
☐ entregado posteriormente a esta Administración en forma legible por computador
☐ La declaración de que el listado de secuencias posteriormente entregado no va más allá de lo divulgado en la solicitud internacional originalmente presentada, ha sido entregada.
☐ La declaración de que la información grabada en la forma legible por computador es idéntica al listado de secuencias escrito que se ha entregado.

4. ☐ Las modificaciones han dado como resultado la cancelación de:

- ☐ la descripción, páginas _____,
☐ las reivindicaciones, Nos. _____,
☐ los dibujos, página _____.

5. ☐ Este reporte ha sido establecido como si (parte de) las modificaciones no se hubieran realizado, ya que éstas han sido consideradas como una ampliación de lo inicialmente divulgado como se indica en la Casilla Suplementaria (Regla 70.2(c)).**

Cualquier hoja de reemplazo que contenga dichas modificaciones deberá ser referida bajo el punto 1 y anexada a este Informe.

III. No establecimiento de opinión con respecto a la novedad, nivel inventivo y aplicabilidad Industrial.

1. La pregunta de si la invención reivindicada parece tener novedad, nivel inventivo (que no sea obvia), o que sea aplicable industrialmente no ha sido examinada con respecto a:

- ☐ la solicitud internacional completa
☒ las reivindicaciones Nos. 7, 8, 11,

Porque

- ☒ la solicitud internacional, o las mencionadas reivindicaciones Nos. _____ se relacionan con los siguientes objetos, los cuales no requieren examen preliminar internacional (*especifique*):

Ver hoja separada

- ☐ la descripción, las reivindicaciones o los dibujos (*Indique los elementos particulares abajo*) o las mencionadas reivindicaciones Nos. _____ son demasiado confusas que no se puede formar ninguna opinión significativa (*especifique*):

- ☐ la descripción, o las mencionadas reivindicaciones Nos. _____ no están adecuadamente soportadas por la descripción que no se puede formar ninguna opinión significativa.

- ☐ no se ha establecido un reporte de búsqueda para las mencionadas reivindicaciones Nos. _____

2. No se pudo realizar un examen preliminar internacional significativo debido a fallas en el listado de nucleótidos y/o aminoácidos para dar cumplimiento con los estándares del Anexo C de las Instrucciones Administrativas:

- ☐ El formato escrito no ha sido suministrado o no cumple con los estándares.

- ☐ El formato de lectura por computador no ha sido suministrado o no cumple con los estándares.

V. Declaración motivada según el Artículo 35(2) en cuanto a la novedad, el nivel inventivo y la aplicación Industrial; citas y explicaciones que apoyan esta declaración.

1. Declaración

Novedad (N)	Reivindicaciones	1-13	SI
	Reivindicaciones		NO
Nivel inventivo (NI)	Reivindicaciones		SI
	Reivindicaciones	1-13	NO
Aplicación Industrial (AI)	Reivindicaciones	1-8, 9, 10, 12, 13	SI
	Reivindicaciones		NO

2. Citas y explicaciones (Regla 70.7)

Ver hoja separada

(III)

Las reivindicaciones 7, 8, 11 se refieren a todos los posibles metabolitos y/o profármacos de la sal del compuesto reclamado y por lo tanto no cumple los requerimientos del Artículo 6 del PCT. Además, en vista del hecho de que dichas reivindicaciones no se encuentran cubiertas por el Informe de Búsqueda no se ha realizado el examen preliminar.

(V)

Habiendo consultado el Informe de Búsqueda Internacional la sal del monoetanosulfonato reivindicado no ha sido revelado en los documentos del arte previo

(D1) WO 01/27081; (D2) WO 01/27080;

(D3) WO 02/081445, un documento P que no es relevante en esta fase, revela derivados estructuralmente similares de indolinas 6-sustituidas sin mencionar sales específicas de los mismos.

Los requerimientos del artículo 33(2) del PCT parecen cumplirse.

El problema que atañe a la invención parece ser el de proporcionar una sal de monoetanosulfonato del compuesto (473) revelado en el documento del arte previo (D1), que tenga propiedades mejoradas como las que se listan en la página 2-3 de la descripción.

El solicitante no ha justificado ninguna de las ventajas sobre el arte previo más cercano Eje. 473 de D1. Además, aunque las reivindicaciones 7, 8 y 11 no se encuentren cubiertas por el Informe de Búsqueda, es de notar que las ventajas inesperadas de la sal reclamada, debido a sus propiedades fisicoquímicas, no pertenecerían al mismo concepto inventivo de cualquiera de los profármacos y/o metabolitos de la sustancia por sí misma.

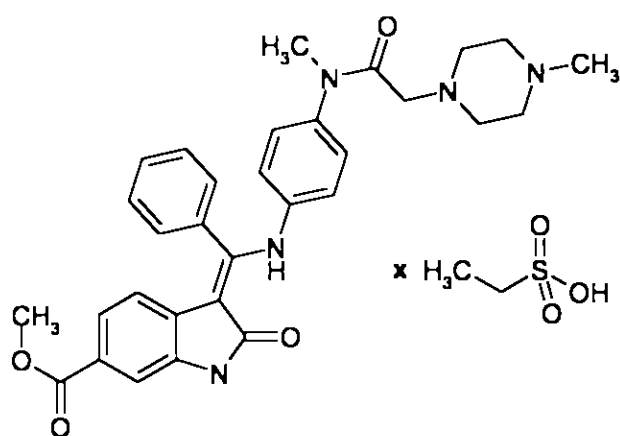
Los requerimientos del Artículo 33(3) del PCT no parecen cumplirse.

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Monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilén]-6-metoxycarbonil-2-Indolnona y su utilización como medicamento

El objeto del presente invento es el compuesto monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilén]-6-metoxycarbonil-2-Indolnona de la fórmula I y su utilización en un medicamento.

Fórmula I:



10 Fundamentos del invento

En el estado actual de la técnica ya se conoce una serie de derivados de 2-Indolnona. Así, por ejemplo, la solicitud de patente Internacional WO 01/27081 da a conocer derivados de 2-Indolnona que poseen valiosas propiedades farmacológicas.

Igualmente que los derivados de 2-Indolnona citados en el estado actual de la técnica, el compuesto de la fórmula I muestra también, especialmente, un efecto inhibidor sobre diferentes quinasas, ante todo, sobre receptores de tirosina-quinasas tales como VEGFR1, VEGFR2, VEGFR3, PDGFR α , PDGFR β , FGFR1, FGFR3, EGFR, HER2, c-Kit, IGF1R, Flt-3 y HGFR, así como sobre la proliferación de células humanas cultivadas, especialmente la de las células endoteliales, por ejemplo en el caso de angiogénesis, pero también sobre la proliferación de otras células, especialmente de células tumorales.

Las valiosas propiedades farmacológicas de los derivados de Indolnona, anteriormente citadas, dadas a conocer en el estado actual de la técnica, representan la premisa fundamental para una eficaz utilización de los compuestos como medicamentos. No obstante, un principio activo tiene que cumplir, además, con otras exigencias para poder ser empleado como medicamento. Estos parámetros están relacionados, en su mayor parte, con la cualidad fisicoquímica del principio activo.

Sin limitación a esto, ejemplos de estos parámetros son la estabilidad de la eficacia de la sustancia de partida bajo diferentes condiciones medioambientales, la estabilidad en el transcurso de la preparación de la formulación farmacéutica, así como la estabilidad de las composiciones finales del medicamento. El principio activo medicamentoso utilizado para la preparación de las composiciones medicamentosas debería presentar, por lo tanto, una elevada estabilidad, que tiene que estar garantizada incluso bajo diferentes condiciones medioambientales. Esto es obligatoriamente necesario para impedir que se utilicen composiciones medicamentosas en las que, junto al verdadero principio activo, estén contenidos, por ejemplo, productos de degradación del mismo. En este caso, un contenido preestablecido de principio activo en las formulaciones farmacéuticas podría ser menor que el especificado.

La absorción de humedad reduce el contenido en principio activo medicamentoso debido al aumento de peso provocado por la admisión de agua. Los medicamentos que tienden a la absorción de humedad se tienen que proteger de la humedad durante el almacenamiento, por ejemplo por adición de agentes de secado adecuados o por almacenamiento del medicamento en un ambiente protegido contra la humedad. Además, la absorción de humedad puede reducir el contenido de principio activo medicamentoso durante la preparación, cuando el medicamento se expone al medio ambiente sin protección alguna contra la humedad. Por lo tanto, preferentemente, un principio activo medicamentoso sólo debería ser higroscópico en escasa medida.

Puesto que la modificación cristalina de un principio activo es importante para la reproducibilidad del contenido en principio activo de una forma de administración, existe la necesidad de esclarecer del mejor modo posible el polimorfismo eventualmente existente de un principio activo que se presente en forma cristalina. Siempre que aparezcan diferentes modificaciones polimorfas de un principio activo, se debería garantizar que la modificación cristalina de la sustancia no varíe en el posterior preparado del medicamento. De otro modo, esto podría influir desventajosamente sobre la eficacia reproducible del medicamento. Ante este panorama, son preferidos principios activos que se caractericen por sólo un escaso polimorfismo.

Otro criterio, el cual bajo ciertas condiciones es de primordial importancia según la elección de la formulación o la elección del procedimiento de preparación, es la solubilidad del principio activo. Si se preparan, por ejemplo, soluciones

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medicamentosas (por ejemplo para infusiones), entonces es imprescindible una suficiente solubilidad del principio activo en disolventes fisiológicamente tolerables. También para medicamentos que se han de administrar por vía oral es de gran importancia una suficiente solubilidad del principio activo.

- 5 El presente invento se fundamenta en la misión de poner a disposición un principio activo medicamentoso, el cual se caracterice no sólo por una elevada eficacia farmacológica sino, además, cumpla lo mejor posible con las exigencias fisicoquímicas citadas anteriormente.

Descripción detallada del invento

- 10 Sorprendentemente, se encontró que el problema citado anteriormente se soluciona con la sal monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-Indolinona de la fórmula I.

- 15 El monoetanosulfonato conforme al invento se caracteriza por su buen carácter cristalino y una escasa formación de producto amorfo al molerlo y prensarlo. Además, no es higroscópico y se disuelve muy bien en disolventes fisiológicamente tolerables.

- La forma cristalina del monoetanosulfonato del compuesto
3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-Indolinona, conforme al invento, se caracteriza por un
20 punto de fusión de $T_{p.f.} = 305 \pm 5^\circ\text{C}$ (determinado por DSC = calorimetría diferencial de barrido (Differential Scanning Calorimetry)); evaluación a través del pico máximo; tasa de calentamiento: $10^\circ\text{C}/\text{min}$). El valor indicado se obtuvo mediante un DSC 821^o de la razón social Mettler Toledo.

- Por lo tanto, un primer objeto del presente invento es la sal
25 monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-indolinona, preferentemente en forma cristalina, caracterizada por un punto de fusión de $T_{p.f.} = 305 \pm 5^\circ\text{C}$ (determinado por DSC; evaluación a través del pico máximo; tasa de calentamiento: $10^\circ\text{C}/\text{min}$).

- La forma cristalina del monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-
30 Indolinona conforme al invento se examinó con más detalle mediante la difracción de polvo de rayos X. El diagrama obtenido se ha representado en la Figura 1.

La siguiente Tabla muestra los datos obtenidos en este análisis.

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Tabla 1: reflejos de polvo de rayos X e intensidades (normalizadas) del monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-Il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-Indolirona

h	k	l	2 θ [°]	Valor d_{hkl} [Å]	Intensidad [%]
0	0	1	7,70	11,47	17,7
0	-1	0	8,78	10,07	19,2
-1	0	1	9,47	9,33	28,4
1	0	1	9,82	9,00	32,2
2	0	0	11,59	7,63	30,9
0	-2	1	11,93	7,41	26,3
1	2	0	13,15	6,73	29,6
-2	0	1	13,69	6,47	31,8
2	1	0	14,17	6,24	30,9
3	-1	0	18,32	5,43	41,7
0	1	2	18,72	5,30	29,0
-1	1	2	16,92	5,238	9,8
3	0	0	17,43	5,08	42,7
2	2	0	17,77	4,99	26,9
1	-4	0	18,58	4,77	31,1
-3	0	1	18,81	4,71	41,8
-2	0	2	19,03	4,66	39,2
3	-3	1	19,73	4,50	40,2
0	4	0	19,87	4,47	6,2
2	-4	1	20,03	4,43	100,0
0	-4	1	20,61	4,31	8,3
-3	-1	1	20,83	4,26	5,5

h	k	l	2θ [°]	Valor d_{hkl} [Å]	Intensidad [%]
1	2	2	21,26	4,18	31,1
-1	3	2	21,76	4,08	19,8
0	4	1	22,05	4,03	32,4
3	-4	1	22,19	4,00	10,1
0	3	2	22,57	3,94	25,6
-3	4	1	23,10	3,85	32,3
-1	0	3	23,81	3,73	32,0
1	4	1	24,69	3,60	26,6
1	3	2	24,78	3,58	24,6
0	5	0	24,91	3,572	15,6
-1	5	1	25,42	3,50	23,7
-4	4	1	26,24	3,39	24,8
3	-2	2	26,91	3,31	22,9
-3	4	2	27,19	3,28	23,9
1	5	0	27,61	3,23	22,0
-1	-5	1	27,95	3,19	22,3
3	-1	3	28,71	3,11	22,1
5	0	0	29,25	3,05	20,2

En la Tabla 1 anterior, el valor " 2θ [°]" representa el ángulo de refracción en grados, y el valor " d_{hkl} [Å]", las distancias entre los planos de la red determinadas en Å.

En el marco del presente invento, el diagrama de polvo de rayos X se obtuvo mediante un difractómetro Bruker D8 Advanced, equipado con un detector sensible a la orientación (OED) y un ánodo de Cu como fuente de rayos X (radiación $\text{CuK}\alpha$, $\lambda = 1,54056 \text{ Å}$, 40 kV, 40 mA).

De forma correspondiente a los datos hallados, representados en la Tabla 1, el presente invento se refiere al monoetanosulfonato cristalino de 3-Z-[1-(4-(N-(4-metil-

piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-indolinona, caracterizado porque en el diagrama de polvo de rayos X presenta, entre otros, los valores característicos $d = 5,43 \text{ \AA}$, $5,08 \text{ \AA}$, $4,71 \text{ \AA}$, $4,50 \text{ \AA}$ y $4,43 \text{ \AA}$ con una intensidad superior al 40%.

5 La evaluación de los datos de polvo de rayos X proporciona la celda unitaria del compuesto conforme al invento, cuyos datos cristalográficos se reproducen en la siguiente Tabla 2:

Fórmula	$C_{88}H_{78}N_{10}O_{16}S_2$
Peso molecular	1315,52
Sistema cristalino	triclínico
a	16,332 Å
b	19,199 Å
c	11,503 Å
α	95,27°
β	90,13°
γ	110,83°
V	3354,4 Å ³

10 La celda unitaria se define por las longitudes de los lados a, b y c de esta celda, por los ángulos relativos α , β y γ de los lados de las celdas entre sí, así como por el volumen V (véase Tabla 2). Métodos para obtener y evaluar diagramas de polvo de rayos X para la determinación de celdas unitarias y sus dimensiones son conocidas en el estado actual de la técnica y se reconocen para la caracterización de la naturaleza cristalina y la estructura de un producto.

15 Otro objeto del presente invento es, por lo tanto, el monoetanosulfonato cristalino de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-indolinona conforme al invento, caracterizado por una celda unitaria determinada mediante mediciones difractométricas de polvo de rayos X, con las siguientes dimensiones:

20 a = 16,332 Å
b = 19,199 Å
c = 11,503 Å

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$\alpha = 85,27^\circ$
 $\beta = 90,13^\circ$
 $\gamma = 110,83^\circ$ y
 $V = 3354,4 \text{ \AA}^3$

5 Con ayuda de un monocristal se pudo calcular, además, el grupo espacial del compuesto conforme al invento. Los datos correspondientes se indican en la siguiente Tabla 3:

Solución estructural	A partir de los datos del cristal unitario
Grupo espacial	$P\bar{1}$ (#2)
Densidad (calculada)	2,605 g/ cm ³
Contenido de la celda	2 moléculas con distinta conformación 2 x EtSO ₄ 1 x H ₂ O

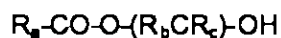
10 Bajo condiciones normales, el monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-Indolinona conforme al invento se presenta en forma de semihidrato, del cual a una temperatura de aproximadamente 130°C se evade agua. La Figura 2 reproduce el termooanálisis.

15 El objeto del presente invento son también los metabolitos del compuesto monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-Indolinona de fórmula I, a promedicamentos de este compuesto o de estos metabolitos obtenidos mediante, por ejemplo, derivatización química o no química de toda la molécula o de uno o más grupos químicos en la molécula, y a su uso en un medicamento.

20 Por tanto, los metabolitos del compuesto monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-Indolinona se pueden obtener mediante, por ejemplo, desesterificación de un grupo éster en la molécula. Esta desesterificación puede tener lugar *in vivo* por la acción de esterasas específicas o no específicas presentes en el
25 cuerpo del paciente al que se administra el medicamento.

Los promedicamentos del compuesto monoetanosulfonato de 3-Z-[1-(4-(N-(4-metil-piperazina-1-il)-metilcarbonyl)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonyl-2-indolinona o de sus metabolitos se pueden obtener mediante, por ejemplo, cualquier sustitución química de un grupo carboxi o amino presente en la molécula, o por sustitución del átomo N-1 del resto indolinona por un grupo que se puede disociar *in vivo*.

Por un grupo que se puede disociar *in vivo* y convertir *in vivo* en un grupo carboxi, se entiende por ejemplo un grupo hidroximetilo, un grupo carboxil esterificado con un alcohol en el que el resto alcohólico denota preferiblemente un alcohol C₁₋₆, un fenil-C₁₋₃-alcohol, un cicloalcohol C₃₋₆, mientras que un cicloalcohol C₃₋₆ se puede sustituir adicionalmente por uno o dos grupos alquilo C₁₋₃, un cicloalcohol C₃₋₆, en el que un grupo metileno se sustituye en la posición 3 ó 4 por un átomo de oxígeno o por un grupo imino sustituido opcionalmente por un grupo alquilo C₁₋₃, fenil-C₁₋₃-alquilo, fenil-C₁₋₃-alcoyl-carbonilo o C₁₋₆-alquil-carbonilo, y el resto cicloalcohol se puede sustituir adicionalmente por uno o dos grupos alquilo C₁₋₃, un cicloalquénol C₄₋₇, un alquénol C₃₋₆, un fenil-C₃₋₆-alquénol, un alquénol C₃₋₆ o fenil-C₃₋₆-alquénol, con la condición de que no haya un enlace al átomo de oxígeno desde un átomo de carbono que soporta un enlace doble o triple, un C₃₋₆-cicloalquil-C₁₋₃-alcohol, un bicicloalcohol con un total de 8 a 10 átomos de carbono que pueden estar sustituidos adicionalmente en el resto bicicloalquilo por uno o dos grupos alquilo C₁₋₃, un 1,3-dihidro-3-oxo-1-isobenzofuranol o un alcohol de fórmula



en la que

R_a se refiere a un grupo alquilo C₁₋₆, cicloalquilo C₆₋₇, fenilo o fenil-C₁₋₃-alquilo,

R_b se refiere a un átomo de hidrógeno, un grupo alquilo C₁₋₃, un cicloalquilo C₆₋₇, o fenilo y

R_c se refiere a un átomo de hidrógeno o un grupo alquilo C₁₋₃,

y por un grupo que se puede disociar *in vivo* a partir de un grupo amino o del átomo N-1 del resto indolinona, se entiende por ejemplo un grupo hidroxilo, un grupo acilo tal como el grupo benzoylo o piridinilo, o un grupo C₁₋₁₆-alquil-carbonilo, tal como el grupo formilo, acetilo, propionilo, butanilo, pentanilo o hexanilo, un grupo aliloxycarbonilo, un grupo C₁₋₁₆-alcoyl-carbonilo tal como el grupo metoxycarbonilo, etoxycarbonilo, propoxycarbonilo, isopropoxycarbonilo, butoxycarbonilo, tert-butoxycarbonilo, pentoxycarbonilo, hexiloxycarbonilo, octiloxycarbonilo, noniloxycarbonilo, deciloxycarbonilo, undeciloxycarbonilo, dodeciloxycarbonilo o hexadeciloxycarbonilo, un

grupo fenil-C₁₋₄-alcoxi-carbonilo tal como el grupo benciloxycarbonilo, feniletoxycarbonilo o fenilpropoxycarbonilo, un C₁₋₃-alquilsulfonil-C₁₋₄-alcoxi-carbonilo, C₁₋₃-alcoxi-C₂₋₄-alcoxi-C₂₋₄-alcoxi-carbonilo o grupo R_aCO-O-(R_bCR_c)-O-CO en el que

R_a se refiere a un grupo alquilo C₁₋₆, cicloalquilo C₃₋₇, fenilo o fenil-C₁₋₃-alquilo,

5 R_b se refiere a un átomo de hidrógeno, un grupo alquilo C₁₋₃, un cicloalquilo C₃₋₇, o fenilo y

R_c se refiere a un átomo de hidrógeno, un grupo alquilo C₁₋₃, o R_aCO-O-(R_bCR_c)-O en el que R_a a R_c son como se han definido anteriormente,

10 y adicionalmente el grupo itálimido, mientras que los grupos éster mencionados previamente se pueden usar también como un grupo que se puede convertir *in vivo* en un grupo carboxil.

Los grupos de promedicamentos preferidos para un grupo carboxi incluyen un grupo C₁₋₄-alcoxi-carbonilo tal como el grupo metoxycarbonilo, etoxycarbonilo, n-propiloxycarbonilo, isopropiloxycarbonilo, n-butiloxycarbonilo, n-pentiloxycarbonilo, n-hexiloxycarbonilo o ciclohexiloxycarbonilo, o un grupo fenil-C₁₋₃-alcoxi-carbonilo tal como el grupo benciloxycarbonilo y

15 para un grupo amino o el grupo N-1 del resto indolnona, un grupo C₁₋₄-alcoxi-carbonilo tal como el grupo metoxycarbonilo, etoxycarbonilo, n-propiloxycarbonilo, isopropiloxycarbonilo, n-butiloxycarbonilo, n-pentiloxycarbonilo, n-hexiloxycarbonilo, ciclohexiloxycarbonilo, n-heptiloxycarbonilo, n-octiloxycarbonilo o n-noniloxycarbonilo, un grupo fenil-C₁₋₃-alcoxi-carbonilo tal como el grupo benciloxycarbonilo, un grupo fenilcarbonilo sustituido opcionalmente por un grupo alquilo C₁₋₃ tal como el grupo benzilo o 4-etil-benzilo, un grupo piridinilo tal como el grupo nicotinilo, un grupo C₁₋₃-alquilsulfonil-n-C₂₋₃-alcoxi-carbonilo o C₁₋₃-alcoxi-C₂₋₃-alcoxi-C₁₋₄-alcoxi-carbonilo, 20 tal como el grupo 2-metilsulfoniletoxicarbonilo o 2-(2-etoxi)-etoxycarbonilo.

Además, los restos alquilo y alcoxi saturados que contienen más de 2 átomos de carbono mencionados en las definiciones anteriores, así como los restos alcanilo y alquilo insaturado que contienen más de 3 átomos de carbono, incluyen también sus isómeros ramificados tales como el grupo isopropilo, tert-butilo, isobutilo, etc.

30 Para la síntesis química de los metabolitos y promedicamentos mencionados previamente, se hace referencia al documento WO 01/27081.

Los estudios experimentales han demostrado que un metabolito del compuesto monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-indolnona es la 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-carbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-carboxil-2-

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Indolnona desesterificada. Se ha evaluado la actividad inhibitoria in vitro de este metabolito sobre diferentes quinasas, usando ensayos de inhibición de quinasas estándar conocidos, así como un ensayo de inhibición de proliferación celular estándar conocido (Inhibición de la proliferación de células endoteliales del cordón umbilical humano estimulada por el VEGF, el denominado "ensayo celular HUVEC"). Estos resultados experimentales han demostrado que este metabolito inhibe diferentes quinasas, tales como VEGFR-2, VEGFR-3, Her-2, FGFR-1, PDGFR-alfa o InsR, así como la proliferación de células estimuladas por VEGF HUVEC.

Además, los compuestos según el presente invento se puede administrar a un paciente que lo necesite en cualquier tipo de forma galénica tal como comprimidos, cápsulas o en una formulación líquida.

Una formulación farmacéutica especialmente adecuada para los compuestos según el presente invento son las cápsulas de gelatina blandas. Las cápsulas de gelatina blandas adecuadas para hacer cápsulas de medicamentos y el procedimiento para su preparación se describe, por ejemplo, en la patente Inglesa nº 395546, la patente de E.E.U.U nº 2.720.463, la patente de E.E.U.U 2.870.062, la patente de E.E.U.U nº 4.829.057, y en las siguientes publicaciones: ANON (Verpack-Rundsch., Vol 21, nº 1, Enero 1970, pag. 136-138), Lachman et al. (The Theory and Practice of Industrial Pharmacy, Cap 13, publicado por Lea & Febiger, 1970), Ebert (Soft Gelatine Capsules: A Unique Dosage Form, reprint from Pharmaceutical Technology, Oct. 1977) y R.F. Jlmerson (Soft Gelatine Capsule Update, Drug Development and Industrial Pharmacy, Vol. 12 (8 & 9), pag. 1133-1144, 1986).

Parte experimental

Los datos de la HPLC (cromatografía de líquidos de elevada resolución) indicados se midieron bajo los parámetros señalados a continuación:

Columna: Inertsil ODS-2, 5 µm x 4,0 mm; disolvente A: solución acuosa al 0,2% de KH₂PO₄, ajustada con lejía de sosa diluida a pH = 6,0; disolvente B: acetonitrilo; temperatura de la columna: 45°C; caudal: 1 ml/min; sistema de gradiente: en el espacio de 5 minutos desde 5% a 30% de disolvente B, después mantener durante 1 minuto al 30% de disolvente B y, a continuación, mantener durante 9 minutos al 55% de disolvente B y, después, mantener durante 4 minutos al 55% de B; concentración de la solución de muestra: 5 mg/ml en acetonitrilo/agua = 3 : 7; volumen de inyección: 3 µl; detección a 225 nm y, respectivamente, 210 nm.

Ejemplo 1

3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-Indolinona

- 5
- 10
- 15
- 20
- 10,5 g (30,0 mmol) de 1-acetil-3-(1-etoxi-1-fenil-metilen)-6-metoxycarbonil-2-Indolinona (para su preparacón véase el documento WO 01/27081 citado al comienzo) y 8,60 g (33,0 mmol) de (N-[(4-metil-piperazina-1-il)-metilcarbonil]-N-metil-p-fenilendlamina (para su preparacón véase el documento WO 01/27081 citado al comienzo) se disuelven en 80 ml de dimetilformamida y se agitan durante 1 hora a 80°C. Después de enfriar, se añaden 6,50 ml de piperidina y se sigue agitando durante dos horas más. Se añade agua, el precipitado formado se filtra con succión y se lava después con un poco de agua. El residuo se suspende en 200 ml de metanol, se filtra con succión y se lava con agua fría y dietiléter. La sustancia se seca al vacío a 110°C.
- Rendimiento: 12,4 g (77% del valor teórico),
Espectro IR: 1610, 1655, 1711 cm⁻¹
T_{p.t.} = 253°C
Fórmula empírica: C₃₁H₃₃N₅O₄
Espectro de masas ESI: m/z = 540 [M+H]⁺
- Análisis elemental: calculado: C 68,99 H 6,16 N 12,98
hallado: C 68,32 H 6,29 N 12,85

Ejemplo 2

25 Monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-indolinona

- 30
- 35
- 605 g (1,12 mol) de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-indolinona se suspenden en 9 litros de metanol y se calientan a 50°C. Se añaden 183,7 g (1,121 mol) de una solución acuosa de ácido etanosulfónico al 70%. La solución que se forma se enfría a 40°C y se mezcla con 4,5 litros de terc-butilmetiléter. Al cabo de unos minutos comienza la cristalización. Para conseguir una precipitación total, se sigue agitando durante 16 horas a la temperatura ambiente. Después de enfriar a 10°C se filtra con succión, se sigue lavando con 2 litros de terc-butilmetiléter y se seca al vacío a 40°C.

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Rendimiento: 638 g (87,6% del valor teórico),
 $T_{p.f.} = 305 \pm 5^{\circ}\text{C}$ (DSC 10 K/min)
 Pureza según la HPLC: 99,4%
 Contenido en agua: 1,0 a 2,0% (KF)

5

Breve descripción de las figuras

La Figura 1 muestra el difractograma de rayos X de polvo de monoetanosulfonato cristalino de 3- -Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-Indolnona.

10

La Figura 2 muestra el termooanálisis y la determinación del punto de fusión (DSC) del monoetanosulfonato cristalino de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-Indolnona .

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85Reivindicaciones

1. Monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-indolinona.
2. Monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-indolinona conforme a la reivindicación 1, en forma cristalina, caracterizado por un punto de fusión de $T_{p.f.} = 305 \pm 5^\circ\text{C}$ (determinado a través DSC; evaluación a través del pico máximo; tasa de calentamiento: $10^\circ\text{C}/\text{min}$).
3. Monoetanosulfonato cristalino de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-indolinona conforme a la reivindicación 2, caracterizado porque en el diagrama por rayos X del polvo presenta, entre otros, los valores característicos $d = 5,43 \text{ \AA}$, $5,08 \text{ \AA}$, $4,71 \text{ \AA}$, $4,50 \text{ \AA}$ y $4,43 \text{ \AA}$ con una intensidad superior al 40%.
4. Monoetanosulfonato cristalino de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-indolinona conforme a la reivindicación 2, caracterizado por una celda unitaria determinada mediante mediciones difractométricas de polvo de rayos X, con las siguientes dimensiones:
 $a = 18,332 \text{ \AA}$
 $b = 19,199 \text{ \AA}$
 $c = 11,503 \text{ \AA}$
 $\alpha = 95,27^\circ$
 $\beta = 90,13^\circ$
 $\gamma = 110,83^\circ$ y
 $V = 3354,4 \text{ \AA}^3$
5. Monoetanosulfonato cristalino de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-indolinona conforme a una de las reivindicaciones 2 a 4, caracterizado porque se presenta en forma de semihidrato.
6. Medicamento que contiene la sal monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-indolinona conforme a una de las reivindicaciones 1 a 5, eventualmente junto a una o varias sustancias de soporte y/o diluyentes.
7. Un metabolito de la sal monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-

2-indolinona.

8. Un promedicamento de la sal monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-indolinona, conforme a una de las reivindicaciones 1 a 5, o de un
5 metabolito conforme a la reivindicación 7.

9. Medicamento que contiene un metabolito conforme a la reivindicación 7 o un promedicamento conforme a la reivindicación 8, opcionalmente junto con una o más sustancias de soporte y/o diluyentes inertes.

10. Utilización del monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-
10 Indolinona conforme a una de las reivindicaciones 1 a 5 para la preparación de un medicamento adecuado para el tratamiento de la proliferación celular excesiva o anormal.

11. Utilización de un metabolito conforme a la reivindicación 7 o un
15 promedicamento conforme a la reivindicación 8, para la preparación de un medicamento adecuado para el tratamiento de la proliferación celular excesiva o anormal.

12. Procedimiento para la preparación de un medicamento conforme a la reivindicación 6, caracterizado por que, por vía no química, la sal monoetanosulfonato
20 de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-indolinona conforme a una de las reivindicaciones 1 a 5, se incorpora en una o más sustancias de soporte y/o diluyentes inertes.

13. Procedimiento para la preparación de un medicamento conforme a la reivindicación 6, caracterizado por que, por vía no química, se incorpora un metabolito
25 conforme a la reivindicación 7 o un promedicamento conforme a la reivindicación 8, en una o más sustancias de soporte y/o diluyentes inertes.

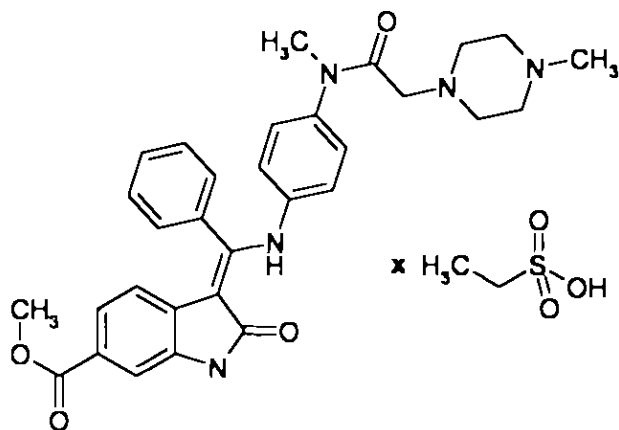
30

88
82

Resumen

Objeto del presente invento es el compuesto monoetanosulfonato de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilan]-6-metoxycarbonil-2-Indolnona de la fórmula I y su utilización como medicamento.

Fórmula I:



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25 PRP/WPC13736/ID-000388

Figura 1: Difractograma de polvo de rayos X del monoetanosulfonato cristalino de 3-Z-[1-(4-(N-((4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxycarbonil-2-Indolinona.

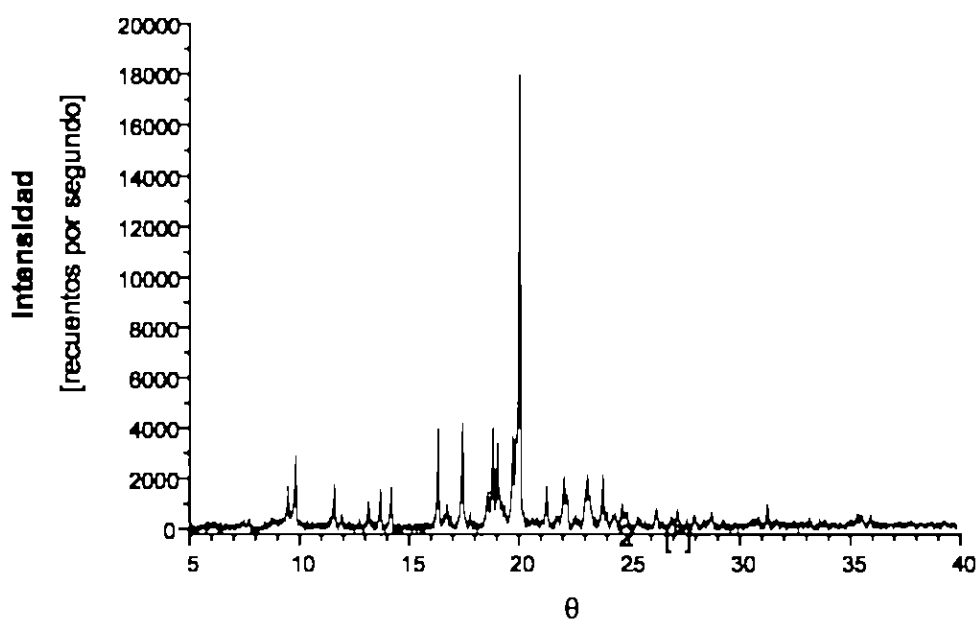
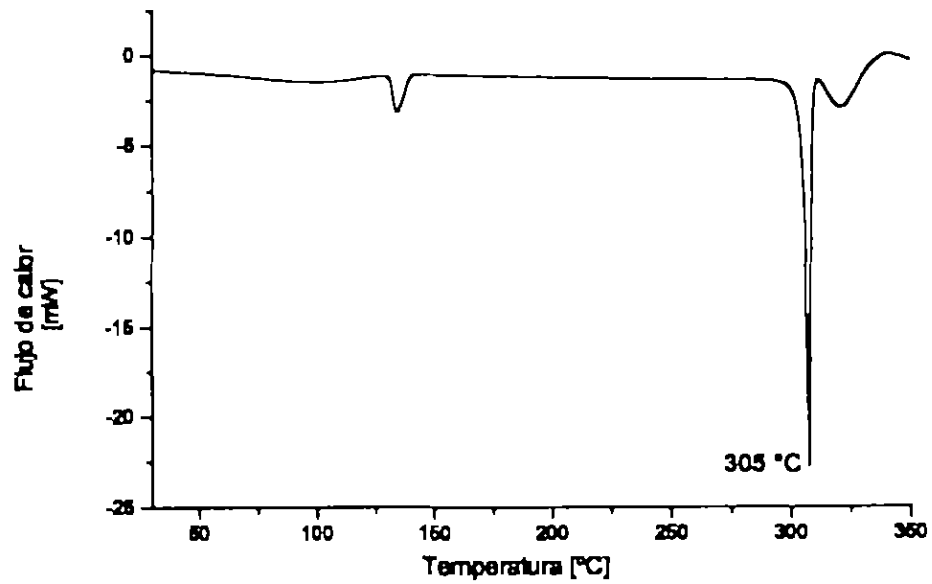


Figura 2: Termoanálisis y determinación del punto de fusión (DSC) del monoetanosulfonato cristalino de 3-Z-[1-(4-(N-(4-metil-piperazina-1-il)-metilcarbonil)-N-metil-amino)-anilino)-1-fenil-metilen]-6-metoxicarbonil-2-indolnona.





FORMATO DE DIGITALIZACION
RELACION DE ANEXOS



Royal
Technologies S.A.
Desarrollo de Software y Servicios

90

Expediente No		05019115	No de Folia
Item		No de unidades	
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA	X	7
9	SOBRE BLANCO TAMAÑO OFICIO		✓
10	OTROS:		

Observaciones:

contiene Ark final

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a1

RECIBO OFICIAL DE CAJA : 05 - 8,795
FECHA : FEBRERO 7 DE 2005

SUPERINDUSTRIA Y COMERCIO
Radicacion : 85817115 00000000 Folios: 92
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Tramite : 011 PCT-PATENTE 379 FASE NACI 411 PRESENTAC
Dependencia: 2828 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00170-6	33236106	07/02/2005	22,990,000.00

***** 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

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Cdo 13736-841-052-8

93
92

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Radicación : 05017115 00000000 Folios: 92
Fecha (AMD): 2005-02-23 16:41:04
Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2828 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL
TRAMITE

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

Firma Responsable: 

Fecha:



94

Industria y Comercio
SUPERINTENDENCIA

93

3

Folio 159

2020
Bogotá DC

Doctor(a)
EMILIO FERRERO
Apoderado(a)
BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

REFERENCIA:	Radicación No.	05-17115
	Solicitud Internacional	PCT/EP2003/007822
	Fecha inicio fase nacional	24-02-2005
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	069
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC

21 ABR. 2005

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Jefe de la División de Nuevas Creaciones

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