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PATENTE DE INVENCION

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54. TITULO POLIMORFISMO DE U.I DODECAHIDROCICLOPENTA(A) FENANTRENIL ESTER DEL
ACIDO TIOFENCARBOILICO.

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A61P11/00

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DOMICILIO BASILEA, SUIZA

74. APODERADO JIMENA ESCOBAR URIBE

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☒ Patente de Invención ☐ Patente de Modelo de Utilidad

☐ Capítulo I ☒ Capítulo II

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SOLICITANTE
(71)

Nombre: **NOVARTIS AG**

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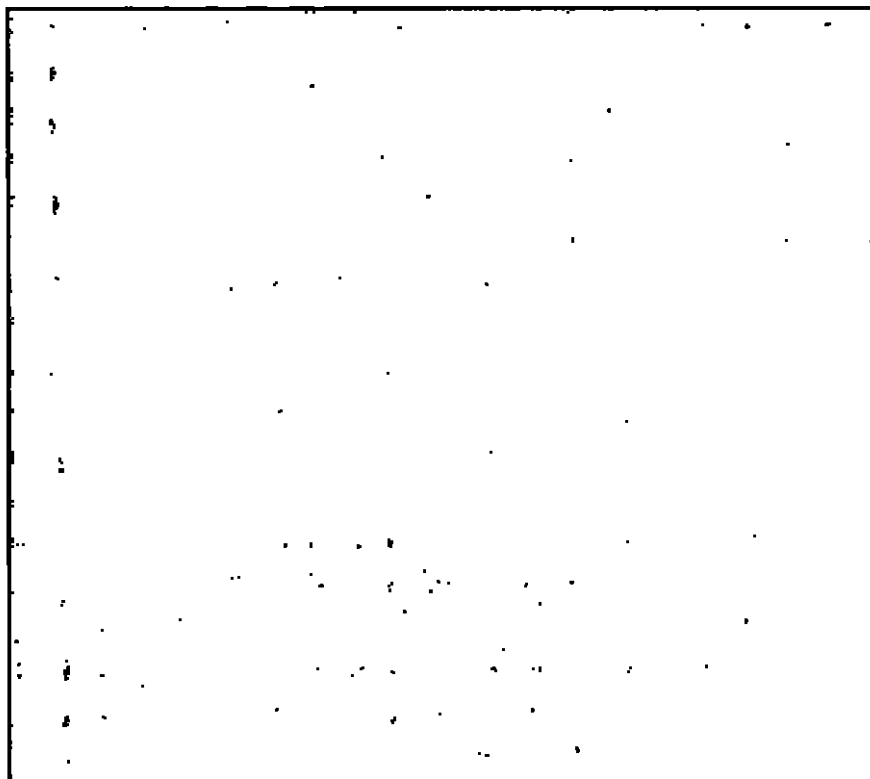
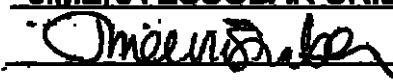
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9 Comprobante de pago No. 05 - 7.300 **Fecha** 31 de enero de 2005

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

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

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

As. 2785/PCT

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SUPERINTENDENCIA Y COMERCIO
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CONCEPTO

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	TOTAL :	\$. 443,000.

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ANEXOS**INVENTORES****1.)****JORDINE, Guido****(Lehener Strasse 148, 79106 Freiburg, Alemania);****2.)****MUTZ. Michael****(Mozartstrasse 33, 79104 Freiburg, Alemania).**

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Solicito expresamente a nombre de la sociedad
NOVARTIS AG, sociedad constituida de conformidad
con las leyes de Suiza, domiciliada en Lichtstrasse 35,
CH-4056 Basilea, Suiza, el otorgamiento de Patente
para la invención titulada "**POLIMORFISMO DE
UN DODECAHIDROCICLOPENTA(A)
FENANTRENIL ESTER DEL ACIDO
TIOFENCARBOXILICO**".

Clase: C07J 33/00


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

RESUMEN

Formas de cristal polimórficas de (6S,9R,10S,11S, 13S,16R,17R)-9-cloro-6-fluoro-11-hidroxi-17-metoxycarbonil-

5 10,13,16-trimetil-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahidro-3H-ciclopenta[a]fenantren-17-iléster del ácido 3-metiltiofen-2-carboxílico. Las formas de cristal poseen actividad anti-inflamatoria, y tienen muy buena estabilidad. También se describen métodos para preparar las formas de cristal.

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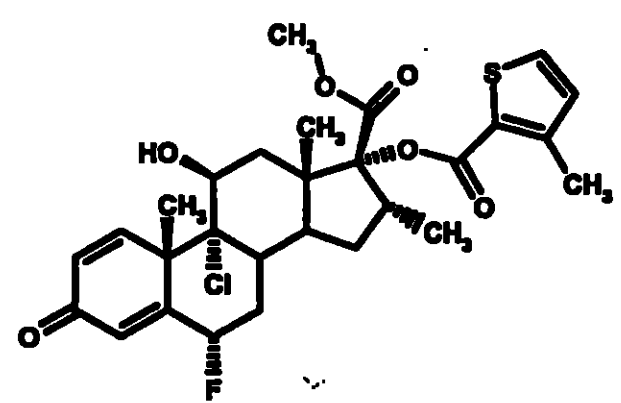
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POLIMORFISMO DE UN DODECAHIDROCICLOPENTA(A)
FENANTRENIL ESTER DEL ACIDO TIOFENCARBOXILICO

Esta invención se refiere a nuevas formas de cristal
 5 polimórficas de un compuesto de la fórmula I, y a métodos para
 prepararlas.

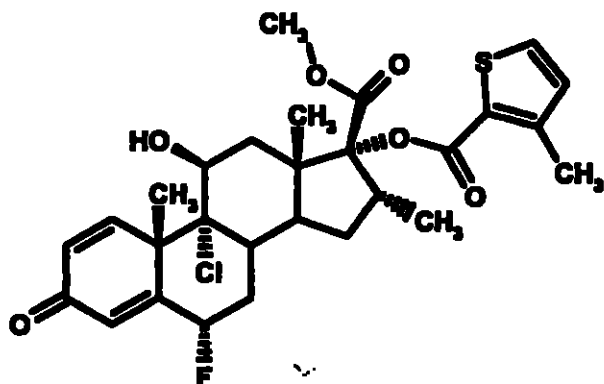
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El compuesto de la fórmula I, es decir,
 15 (6S,9R,10S,11S,13S,16R,17R)-9-cloro-8-fluoro-11-hidroxi-17-
 metoxycarbonil-10,13,16-trimetil-3-oxo-6,7,8,9,10,11,12,13,
 14,15,16,17-dodecahidro-3H-ciclopenta[a]fenantren-17-iléster del
 ácido 3-metiltiofen-2-carboxílico, posee una alta actividad anti-
 inflamatoria. Esta actividad se puede demostrar por su inhibición de
 20 la síntesis de TNF-alfa y liberación en una línea celular de
 macrófagos humanos, y por su inhibición de las condiciones
 inflamatorias, en particular en las vías respiratorias, por ejemplo su
 inhibición de la activación de eosinófilos, en modelos animales, por
 ejemplo, modelos de inflamación de las vías respiratorias de ratón o
 25 de rata, por ejemplo como es descrito por Szarka y colaboradores, J.

5 Este compuesto se ha investigado para utilizarse como un producto farmacéutico. Se ha explorado la existencia de diferentes formas polimórficas de cristalización del compuesto, con el objeto de determinar la forma más apropiada del compuesto para el uso propuesto.

De conformidad con lo anterior, la presente invención
15 proporciona, en un aspecto, un compuesto de la fórmula I:



en una forma de cristal A que tiene un punto de fusión, mediante Calorimetría de Exploración Diferencial, de aproximadamente 264°C con descomposición simultánea, a una velocidad de calentamiento de

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b

20°C/minuto, y las siguientes líneas de difracción características (2 θ en grados angulares $\pm 0.2^\circ$) en el patrón de difracción de rayos X del mismo: 3.6°, 7.3°, 13.4°, 14.6°, 18.3°, 22.0°, 25.8°, 25.9°, 29.5°; ó en una forma de cristal B que tiene un punto de fusión, mediante

5 Calorimetría de Exploración Diferencial, de aproximadamente 270°C con descomposición simultánea, a una velocidad de calentamiento de 20°C/minuto, y las siguientes líneas de difracción características (2 θ en grados angulares $\pm 0.2^\circ$) en el patrón de difracción de rayos X del mismo: 7.2°, 9.3°, 12.0°, 12.8°, 13.1°, 14.5°, 17.4°, 20.4°, 23.2°, y

10 25.8°.

La forma del cristal A se puede preparar mediante la cristalización del compuesto de la fórmula I a partir de una solución del mismo en un solvente orgánico, tal como isopropanol, acetato de etilo, butanol normal, hexano, heptano, terbutilmetiléter, tolueno o

15 tetrahidrofurano, por ejemplo equilibrando el compuesto en ese solvente durante 24 horas a 25°C, o de una manera análoga a la descrita posteriormente en la presente, en el Ejemplo 1. La cristalización se puede inducir, por ejemplo, mediante el enfriamiento de una solución supersaturada del compuesto de la

20 fórmula I en el solvente, o agregando a la solución del compuesto de la fórmula I, un solvente en donde sea menos soluble el compuesto de la fórmula I. La solución de partida del compuesto de la fórmula I puede estar a temperatura ambiente o elevada (hasta el reflujo).

La forma del cristal B se puede preparar mediante la

25 cristalización del compuesto de la fórmula I a partir de una solución

del mismo en un solvente orgánico polar, tal como etanol, metanol, o cloruro de metileno, por ejemplo, equilibrando el compuesto en ese solvente durante 24 horas a 25°C, o de una manera análoga a la descrita posteriormente en la presente en el Ejemplo 2. La
5 cristalización se puede inducir, por ejemplo, mediante el enfriamiento de una solución supersaturada del compuesto de la fórmula I en el solvente polar, o agregando a la solución del compuesto de la fórmula I, un solvente polar en el que sea menos soluble el compuesto de la fórmula I. La solución de partida del
10 compuesto I puede estar a temperatura ambiente o elevada (hasta el reflujo).

Para la preparación de cada una de las formas de cristal, el procesamiento se puede llevar a cabo en general utilizando procedimientos conocidos para la separación del cristalizado a partir
15 del licor madre, por ejemplo mediante filtración, con o sin la asistencia de presión y/o vacío, o mediante centrifugación, y el secado subsecuente del cristalizado.

En la presencia de etanol, la forma del cristal A se
convierte a la forma del cristal B. En la presencia de isopropanol, la
20 forma del cristal B se convierte a la forma del cristal A.

Las formas del cristal se pueden distinguir en particular por sus diagramas en polvo de rayos X. De preferencia se utilizan diagramas de rayos X tomados con un difractómetro y utilizando difracción Cu-K α , para caracterizar los sólidos de los compuestos
25 orgánicos. Los diagramas de difracción en polvo de rayos X son

particularmente útiles para determinar la forma del cristal o la modificación del compuesto de la fórmula I. El uso de estos diagramas se describe en los ejemplos acompañantes.

La forma del cristal A parece ser más
5 termodinámicamente estable que la forma del cristal B en el estado sólido. Sin embargo, en suspensión con solventes, la estabilidad depende del solvente.

El compuesto de la fórmula I se puede preparar de acuerdo con el método dado en el Ejemplo 26 de la Solicitud
10 Internacional de Patente Número WO 02/00679.

Dada su actividad anti-inflamatoria, el compuesto de la fórmula I en la forma del cristal A ó B, es útil en el tratamiento de condiciones inflamatorias, en particular enfermedades inflamatorias u obstructivas de las vías respiratorias. El tratamiento de acuerdo con
15 la invención puede ser sintomático o profiláctico.

Las enfermedades inflamatorias u obstructivas de las vías respiratorias a las que es aplicable la presente invención incluyen asma de cualquier tipo o génesis, incluyendo tanto asma intrínseco (no alérgico) como asma extrínseco (alérgico), asma leve, asma
20 moderado, asma severo, asma bronquítico, asma inducido por ejercicio, asma ocupacional, y asma inducido en seguida de infección bacteriana. También se debe entender que el tratamiento de asma abarca el tratamiento de sujetos, por ejemplo de menos de 4 ó 5 años de edad, que exhiban síntomas de jadeo y que sean
25 diagnosticados o diagnosticables como "bebés jadeantes", una

categoría de paciente establecida de importante preocupación médica y ahora frecuentemente identificada como asmáticos incipientes o de fase temprana. (Para mayor conveniencia, esta condición asmática particular es referida como "síndrome de bebé jadeante"). La eficacia profiláctica en el tratamiento de asma será evidenciada por una frecuencia o severidad reducidas del ataque sintomático, por ejemplo del ataque asmático agudo o broncoconstrictor, mejora en la función pulmonar, o mejor hiperreactividad de las vías respiratorias. Además, se puede evidenciar por un requerimiento reducido de otra terapia sintomática, es decir, terapia para, o pretendida para, restringir o abortar el ataque sintomático cuando se presente, por ejemplo anti-inflamatoria (por ejemplo, corticosteroide) o broncodilatadora. El beneficio profiláctico en asma puede ser aparente en particular en los sujetos susceptibles al "ahogamiento matutino". El "ahogamiento matutino" es un síndrome asmático reconocido, común a un porcentaje sustancial de asmáticos, y caracterizado por un ataque de asma, por ejemplo entre las horas de aproximadamente 4 a 6 a.m., es decir, en un tiempo normalmente distante sustancialmente de cualquier terapia de asma sintomática previamente administrada.

Otras enfermedades y condiciones inflamatorias u obstructivas de las vías respiratorias a las que es aplicable la presente invención incluyen lesión pulmonar aguda (ALI), síndrome de insuficiencia respiratoria de adultos (ARDS), enfermedad pulmonar obstructiva crónica, de las vías respiratorias, o del pulmón

(COPD, COAD, ó COLD), incluyendo bronquitis crónica o dispnea asociada con la misma, enfisema, así como exacerbación de hiperreactividad de las vías respiratorias a consecuencia de otra terapia de fármacos, en particular otra terapia de fármacos inhalados. La invención también es aplicable al tratamiento de bronquitis de cualquier tipo o génesis, incluyendo, por ejemplo, bronquitis aguda, araquídica, catarral, cruposa, crónica o ftinoide. Otras enfermedades inflamatorias u obstructivas de las vías respiratorias a las que es aplicable la presente invención incluyen

neumoconiosis (una enfermedad inflamatoria, comúnmente ocupacional, de los pulmones, frecuentemente acompañada por obstrucción de las vías respiratorias, ya sea crónica o aguda, y ocasionada por la inhalación repetida de polvos) de cualquier tipo o génesis, incluyendo, por ejemplo, aluminosis, antracosis, asbestosis, calicosis, ptilosis, siderosis, silicosis, tabacosis, y bisinosis.

Considerando su actividad anti-inflamatoria, en particular en relación con la inhibición de la activación de eosinófilos, el compuesto de la fórmula I en la forma del cristal A ó B, también es útil en el tratamiento de desórdenes relacionados con eosinófilos, por ejemplo eosinofilia, en particular desórdenes relacionados con eosinófilos de las vías respiratorias (por ejemplo, que involucren infiltración eosinofílica patológica de los tejidos pulmonares), incluyendo hipereosinofilia como afecta a las vías respiratorias y/o a los pulmones, así como, por ejemplo, desórdenes relacionados con eosinófilos de las vías respiratorias a consecuencia o concomitantes

al síndrome de Löffler, neumonía eosinofílica, infestación parasitaria (en particular de metazoarios) (incluyendo eosinofilia tropical), aspergillosis broncopulmonar, poliarteritis nodosa (incluyendo síndrome de Churg-Strauss), granuloma eosinófilico, y desórdenes
5 relacionados con eosinófilos que afecten a las vías respiratorias, ocasionados por reacción a fármacos.

El compuesto de la fórmula I en la forma del cristal A ó B, también es útil en el tratamiento de condiciones inflamatorias de la piel, por ejemplo psoriasis, dermatitis por contacto, dermatitis
10 atópica, alopecia areata, eritema multiforme, dermatitis herpetiformis, escleroderma, vitiligo, angitis de hipersensibilidad, urticaria, penfigoide buloso, lupus eritematoso, pemfigo, epidermólisis bulosa adquirida, y otras condiciones inflamatorias de la piel. El compuesto de la fórmula I en la forma del cristal A ó B,
15 también se puede utilizar para el tratamiento de otras enfermedades o condiciones, en particular enfermedades o condiciones que tengan un componente inflamatorio, por ejemplo el tratamiento de enfermedades y condiciones del ojo, tales como conjuntivitis, queratoconjuntivitis sicca, y conjuntivitis bernal, enfermedades que
20 afecten a la nariz, incluyendo rinitis alérgica, enfermedades de las articulaciones, tales como artritis reumatoide, y enfermedad inflamatoria del intestino, tal como colitis ulcerativa y enfermedad de Crohn.

El compuesto de la fórmula I en la forma del cristal A ó B,
25 también es útil como un agente co-terapéutico para utilizarse en

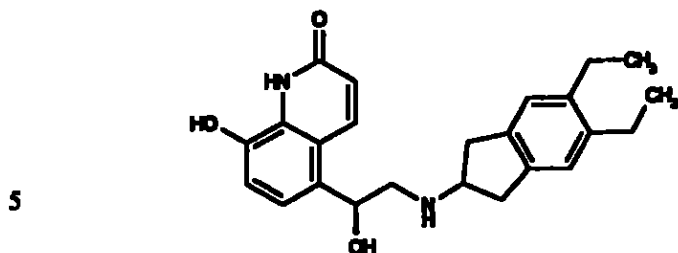
conjunto con otras sustancias de fármaco para el tratamiento de enfermedades de las vías respiratorias, en particular sustancias de fármaco broncodilatadoras o anti-inflamatorias, particularmente en el tratamiento de enfermedades obstructivas o inflamatorias de las vías respiratorias, tales como las mencionadas anteriormente en la presente, por ejemplo como potenciadores de la actividad terapéutica de estos fármacos, o como un medio para reducir la dosificación requerida o los efectos secundarios potenciales de estos fármacos. Los compuestos de la fórmula I en la forma del cristal A ó B, se pueden mezclar con el otro fármaco en una composición farmacéutica fija, o se pueden administrar por separado, antes, simultáneamente con, o después del otro fármaco.

Estos fármacos anti-inflamatorios incluyen esteroides, en particular glucocorticosteroides, tales como budesonida, dipropionato de beclometasona, propionato de fluticasona, ciclesonida, o furoato de mometasona, y los compuestos descritos en las Publicaciones Internacionales Números WO 0200679, WO 0212266 y WO 02100879; antagonistas de LTB₄ tales como los descritos en la Patente de los Estados Unidos de Norteamérica Número US 5451700; antagonistas de LTB₄ tales como los descritos en la Patente de los Estados Unidos de Norteamérica Número US 5451700; antagonistas de LTD₄ tales como montelukast y zafirlukast; agonistas del receptor de dopamina, tales como cabergolina, bromocriptina, ropinirola, y 4-hidroxi-7-[2-[[2-[[3-(2-feniletoksi)-propil]sulfonil]etil]amino]etil]-2(3H)-benzotiazolona y sales farmacéuticamente aceptables de la misma

(siendo el clorhidrato Viozan® - AstraZeneca); inhibidores de PDE4 tales como Ariflo® (GlaxoSmith Kline), Roflumilast (Byk Gulden), V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Scherin-Plough), Arofilline (Almirall Prodesfarma), PD189859 (Parke-Davis), AWD-12-
5 281 (Asta Medica), CDC-801 (Celgene) y KW-4490 (Kyowa Hakko Kogyo); agonistas de A2a tales como los descritos en las Patentes Números 1052264, EP 1241176, WO 0023457, WO 0077018, WO 0123399, WO 0160835, WO 0194368, WO 0200676, WO 0222630, WO 0296462, WO 0127130, WO 0127131, WO 9602543, WO 9602553, WO
10 9828319, WO 9924449, WO 9924450, WO 9924451, WO 9938877, WO 9941267, WO 9967263, WO 9967264, WO 9967265, WO 9967266, WO 9417090, EP 409595A2 y WO 0078774; y antagonistas de A2b tales como los descritos en la Publicación Internacional Número WO 02/42298.

15 Estos fármacos broncodilatadores incluyen agentes anticolinérgicos o antimuscarínicos, tales como los descritos en las Patentes Números EP 424021, US 5171744 (Pfizer), y WO 01/04118 (Almirall Prodesfarma), pero en particular, bromuro de ipratropio, bromuro de oxitropio, y bromuro de tiotropio, y agonistas del
20 adrenoceptor beta-2 tales como salbutamol, terbutalina, salmeterol, y especialmente formoterol y sales farmacéuticamente aceptables de los mismos, y los compuestos (en forma libre o de sal o de solvato) de la fórmula I de la Publicación Internacional del TCP Número WO 00/75114, cuyo documento se incorpora a la presente como
25 referencia, de preferencia los compuestos de los ejemplos de la

misma, en especial un compuesto de la fórmula:



en forma libre o de sal farmacéuticamente aceptable o de solvato.

Se pueden utilizar combinaciones del compuesto de la fórmula I en la forma del cristal A ó B, y agonistas beta-2, inhibidores de PDE4, o antagonistas de LTD4, por ejemplo en el tratamiento de COPD, o en particular de asma.

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Se pueden utilizar combinaciones del compuesto de la fórmula I en la forma del cristal A ó B, y agentes anticolinérgicos o antimuscarínicos, inhibidores de PDE4, antagonistas de LTB4, por ejemplo en el tratamiento de asma, o en particular de COPD.

15

De conformidad con lo anterior, la invención también proporciona un método para el tratamiento de una condición inflamatoria, en particular una enfermedad inflamatoria u obstructiva de las vías respiratorias, el cual comprende administrar a un sujeto, en particular a un sujeto humano, que lo necesite, una cantidad efectiva del compuesto de la fórmula I en la forma del cristal A ó B como se describe anteriormente en la presente. En otro aspecto, la invención proporciona el uso del compuesto de la fórmula I en la forma del cristal A ó B, para la fabricación de un medicamento para el tratamiento de una condición inflamatoria, en particular una

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enfermedad inflamatoria u obstructiva de las vías respiratorias.

El compuesto de la fórmula I en la forma del cristal A ó B, se puede administrar mediante cualquier vía apropiada, por ejemplo oralmente, por ejemplo en la forma de una tableta o cápsula; 5 parenteralmente, por ejemplo intravenosamente; mediante inhalación, por ejemplo en el tratamiento de la enfermedad inflamatoria u obstructiva de las vías respiratorias; intranasalmente, por ejemplo en el tratamiento de rinitis alérgica; tópicamente a la piel, por ejemplo en el tratamiento de dermatitis atópica; rectalmente, por ejemplo en 10 el tratamiento de enfermedad inflamatoria del intestino.

En un aspecto adicional, la invención también proporciona una composición farmacéutica que comprende, como ingrediente activo, al compuesto de la fórmula I en la forma del cristal A ó B, opcionalmente junto con un diluyente o vehículo farmacéuticamente 15 aceptable para el mismo. La composición puede contener un agente co-terapéutico, tal como un fármaco broncodilatador o anti-inflamatorio como se describe anteriormente en la presente. Estas composiciones se pueden preparar utilizando diluyentes o excipientes convencionales y técnicas conocidas en el campo 20 galénico. Por consiguiente, las formas de dosificación oral pueden incluir tabletas y cápsulas. Las formulaciones para administración tópica pueden tomar la forma de cremas, ungüentos, geles, o sistemas de suministro transdérmico, por ejemplo parches. Las composiciones para inhalación pueden comprender formulaciones en 25 aerosol u otras formulaciones atomizables, o formulaciones en polvo

seco.

Cuando la composición comprende una formulación en aerosol, de preferencia contiene, por ejemplo, un propelente de hidrofluoroalcano (HFA), tal como HFA134a ó HFA227, o una mezcla
5 de los mismos, y puede contener uno o más co-solventes conocidos en la técnica, tales como etanol (hasta el 20 por ciento en peso), y/o uno o más tensoactivos, tales como ácido oleico o trioleato de sorbitán, y/o uno o más agentes de volumen, tales como lactosa. Cuando la composición comprende una formulación en polvo seco, de
10 preferencia contiene, por ejemplo, al compuesto de la fórmula I en la forma del cristal A ó B, con un diámetro de partículas de hasta 10 micras, opcionalmente junto con un diluyente o vehículo, tal como lactosa, de la distribución de tamaños de partículas deseada, y un compuesto que ayude a proteger contra el deterioro del desempeño
15 del producto debido a la humedad. Cuando la composición comprende una formulación nebulizada, de preferencia contiene, por ejemplo, al compuesto de la fórmula I en la forma del cristal A ó B, ya sea disuelto, o bien suspendido, en un vehículo que contenga agua, un co-solvente tal como etanol o propilenglicol, y un
20 estabilizante, el cual puede ser un tensoactivo.

La invención incluye (A) el compuesto de la fórmula I en la forma del cristal A ó B en una forma inhalable, por ejemplo en una composición en aerosol u otra composición atomizable, o en un
particulado inhalable, por ejemplo en una forma micronizada, (B) un
25 medicamento inhalable que comprende al compuesto de la fórmula I

en la forma del cristal A ó B en una forma inhalable; (C) un producto farmacéutico que comprende al compuesto de la fórmula I en la forma del cristal A ó B en una forma inhalable, en asociación con un dispositivo de inhalación; y (D) un dispositivo de inhalación que
5 contiene al compuesto de la fórmula I en la forma del cristal A ó B en una forma inhalable.

Las dosificaciones del compuesto de la fórmula I en la forma del cristal A ó B empleadas en la práctica de la presente invención, por supuesto, variarán dependiendo, por ejemplo, de la
10 condición particular que se vaya a tratar, del efecto deseado, y del modo de administración. En general, las dosificaciones diarias adecuadas para administrarse mediante inhalación son del orden de 0.005 a 10 miligramos, mientras que para administración oral, las dosis diarias adecuadas son del orden de 0.05 a 100 miligramos.

15 La invención se ilustra mediante los siguientes ejemplos.

Ejemplo 1

Preparación y caracterización de la Forma del Cristal A

50 miligramos del compuesto de la fórmula I se equilibran
20 en 1 mililitro de isopropanol durante 24 horas a 25°C. El producto se filtra y se seca. Después del secado, se obtiene el compuesto de la fórmula I en la forma de cristales blancos.

Las mediciones se hacen mediante difracción en polvo de rayos X, y utilizando Cu-K α_1 . El patrón de difracción de rayos X así
25 determinado, como está representado por las líneas de reflexión y

las intensidades de las líneas más importantes, se muestra en la Figura 1, y se caracteriza en la siguiente Tabla 1.

TABLA 1

5 **Líneas de difracción de rayos X e Intensidades para la forma del cristal A**

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2θ	Intensidad
3.6	mediana
7.3	fuerte
13.4	mediana
14.6	fuerte
18.3	mediana
22.0	mediana
25.8	fuerte
25.9	mediana
29.5	mediana

Ejemplo 2

20 **Preparación y caracterización de la forma del cristal B**

87 miligramos del compuesto de la fórmula I se equilibran en 2 mililitros de etanol durante 24 horas a 25°C. El producto se filtra y se seca. Después del secado, se obtiene el compuesto de la fórmula I en la forma de cristales blancos.

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Las mediciones se hacen mediante difracción en polvo de

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rayos X y utilizando Cu-k α_1 . El patrón de difracción de rayos X así determinado, como está representado por las líneas de reflexión y las intensidades de las líneas más importantes, se muestra en la Figura 2, y se caracteriza en la siguiente Tabla 2.

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TABLA 2
Líneas de difracclón de rayos X e Intensidades para la forma del cristal B

10	2 θ	Intensidad
	7.2	fuerte
15	9.3	mediana
	12.0	mediana
	12.8	mediana
	13.1	mediana
	14.5	fuerte
20	17.4	mediana
	20.4	mediana
	23.2	mediana
	25.8	mediana

Ejemplo 3

Preparación de las formas de cristal A y B en diferentes solventes

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8 miligramos del compuesto de la fórmula I se equilibran

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con 1.5 mililitros de una variedad de solventes durante cuando
menos 24 horas en un baño de agua a $25^{\circ}\text{C} \pm 0.1$. Las soluciones se
filtran y se secan durante 10 minutos al aire. La parte sólida se
investiga mediante difracción en polvo de rayos X (XRPD) para
5 identificar la forma de cristal producida. Los resultados se muestran
en la siguiente Tabla 3.

El procedimiento se repite a $50^{\circ}\text{C} \pm 0.1$, y a $70^{\circ}\text{C} \pm 0.1$, y
los resultados se muestran en las Tablas 4 y 5, respectivamente.

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TABLA 3
Equilibrio con solvente a 25°C

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Solvente	XRPD
butanol normal	Forma del cristal A
etanol	Forma del cristal B
acetato de etilo	Forma del cristal A
isopropanol	Forma del cristal A
hexano	Forma del cristal A
heptano	Forma del cristal A
metanol	Forma del cristal B
cloruro de metileno	Forma del cristal B
terbutilmetiléter	Forma del cristal A
tolueno	Forma del cristal A
tetrahidrofurano	Forma del cristal A
agua	Formas de cristal A + B

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TABLA 4
Equilibrio con solvente a 50°C

	Solvente	XRPD
5	butanol normal	Forma del cristal A
	etanol	Forma del cristal B
	acetato de etilo	Forma del cristal A
	isopropanol	Forma del cristal A
	hexano	Forma del cristal A
10	heptano	Forma del cristal A
	metanol	Forma del cristal B
	cloruro de metileno	Forma del cristal B
	terbutilmetiléter	Forma del cristal A
	tetrahidrofurano	Forma del cristal A
15	tolueno	Forma del cristal A
	agua	Formas de cristal A + B

TABLA 5
Equilibrio con solvente a 70°C

	Solvente	XRPD
20	butanol normal	Forma del cristal A
	etanol	Forma del cristal B
	isopropanol	Forma del cristal A

Estos resultados muestran que la elección del solvente dicta cuál forma de cristal del compuesto de la fórmula I se forma.

Ejemplo 4

Estabilidad de las formas de cristal A y B

Las muestras del compuesto de la fórmula I en la forma del cristal A, el compuesto de la fórmula I en la forma del cristal B, una mezcla de ambas formas de cristal, y una forma amorfa del compuesto de la fórmula I (obtenida mediante secado por pulverización) se almacenan durante 4 semanas a 80°C bajo diferentes condiciones, y se analizan mediante difracción en polvo de rayos X (XRPD). Los resultados se muestran en la siguiente Tabla 6.

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TABLA 6
Estabilidad después de 4 semanas a 80°C

15	Condiciones	Sellado	75% h.r.* abierto	N₂	N₂ + 2% agua	O₂
	Forma del cristal A	A	A	A	A	A
	Forma del cristal B	B	A+B	B	A+B	A+B
	Formas de cristal A+B	A+B	A+B	A+B	A+B	A+B
20	Forma amorfa	A	A	A	A	A

* humedad relativa

Estos resultados muestran que la forma del cristal B puede convertirse cuando menos parcialmente en el estado sólido, a la forma del cristal A, cuando se almacena durante 4 semanas 80°C.

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La forma amorfa también puede convertirse a la forma del cristal A. Esto sugiere que la forma del cristal A es más termodinámicamente estable que la forma del cristal B.

5 Ejemplo 5

Experimentos de calor de la solución

El calor de la solución de muestras de las formas de cristal A y B del compuesto de la fórmula I se mide a 25°C en acetona. Los resultados se muestran en la siguiente Tabla 7.

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TABLA 7
Calor de la solución a 25°C en acetona

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Forma del cristal	Calor de la solución (J/g)
A	29.3
B	17.9

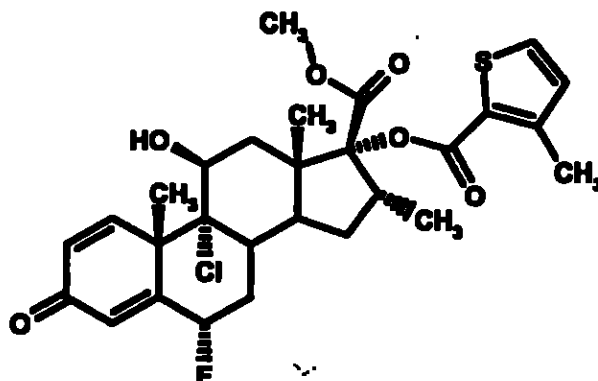
20

Estos resultados muestran que la forma del cristal A tiene un calor endotérmico de la solución más alto comparándose con la forma del cristal B. Esto indica que la forma del cristal A es más termodinámicamente estable que la forma del cristal B.

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REIVINDICACIONES

1. Un compuesto de la fórmula I:



en una forma de cristal B que tiene un punto de fusión, mediante Calorimetría de Exploración Diferencial, de aproximadamente 270°C con descomposición simultánea, a una velocidad de calentamiento de 20°C/minuto, y las siguientes líneas de difracción características (2 θ en grados angulares $\pm$ 0.2°) en el patrón de difracción de rayos X del mismo: 7.2°, 9.3°, 12.0°, 12.8°, 13.1°, 14.5°, 17.4°, 20.4°, 23.2°, y 25.8°.

2. Una composición farmacéutica que comprende, como ingrediente activo, una cantidad efectiva del compuesto de la fórmula I en la forma del cristal A ó B como se define en la reivindicación 1, opcionalmente junto con un vehículo farmacéuticamente aceptable.

3. Una composición de acuerdo con la reivindicación 2, la cual está en una forma inhalable.

4. El uso de un compuesto de acuerdo con la reivindicación 1, en la forma del cristal A ó B, para la preparación de

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un medicamento para el tratamiento de una enfermedad inflamatoria u obstructiva de las vías respiratorias.

5 5. Un método para preparar un compuesto de la fórmula I en la forma del cristal A como se define en la reivindicación 1, el cual comprende cristalizar el compuesto de la fórmula I como se define en la reivindicación 1, a partir de una solución del mismo en etanol, metanol o cloruro de metileno.

10 6. Una forma de cristal del compuesto de la fórmula I, sustancialmente como se describe en la presente con referencia a cualquiera de los ejemplos.

7. Una forma de cristal del compuesto de la fórmula I, sustancialmente como se describe en la presente con referencia a cualquiera de los dibujos.

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PCT

REQUEST

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

For receiving Office use only

PCT/EP 03/08314	
International Application No.	
28.07.03	28 JUL 2003
International Filing Date	
EUROPEAN PATENT OFFICE PCT INTERNATIONAL APPLICATION	
Name of receiving Office and "PCT International Application"	
Applicant's or agent's file reference (if desired) (12 characters maximum) 4-32595A/HO 59	

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Box No. II APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
Novartis AG Lichtstrasse 35 4058 Basel CH	Telephone No. +41 61 324 11 11 Facsimile No. +41 61 322 75 32 Teleprinter No. Applicant's registration No. with the Office
State (that is, country) of nationality: CH	State (that is, country) of residence: CH
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box	
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Novartis Pharma GmbH Brunner Strasse 59 1230 Vienna AT	This person is: ☒ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
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GRUBB, Phillip Novartis AG Corporate Intellectual Property 4002 Basel CH	Telephone No. +41 61 324 11 11 Facsimile No. +41 61 322 75 32 Teleprinter No. Agent's registration No. with the Office
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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	
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State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
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State (that is, country) of nationality:	State (that is, country) of residence:
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Mark the applicable check-boxes below; at least one must be marked.

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- ☒ 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
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- ☐ 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):

- | | | |
|---|--|---|
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Supplemental Box

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

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

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

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

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Novartis Pharma GmbH is applicant for AT (Austria) only.

(ii) If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: In such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) If, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

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32**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) 29 July 2002 (29.07.02)	0217504.0	GB		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

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

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

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

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 | : |

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Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) In paper form, the following number of sheets:

request (including declaration sheets) : 6

description (excluding sequence listings and/or tables related thereto) : 12

claims : 2

abstract : 1

drawings : 1

Sub-total number of sheets : 22

sequence listings : :

tables related thereto : :

(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)

Total number of sheets : 22

(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:

(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)

This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):

1. ☒ fee calculation sheet : 1

2. ☐ original separate power of attorney : 1

3. ☐ original general power of attorney : :

4. ☒ copy of general power of attorney; reference number, if any: AV 38671 : 1

5. ☐ statement explaining lack of signature : :

6. ☐ priority document(s) identified in Box No. VI as item(s): (1) : 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): : :

Figure of the drawings which should accompany the abstract:

Language of filing of the international application:

English

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).

In the name of the applicants

The representative

Philipp Grubb

10.07.2003

GRUBB, Philip AV 38671

For receiving Office use only

1. Date of actual receipt of the purported international application:

28.07.03

28 JUL 2003

2. Drawings:

☒ received:

3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:

☐ not received:

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:

(12) SOLICITUD INTERNACIONAL PUBLICADA DE ACUERDO CON EL TRATADO DE COOPERACION DE PATENTES (PCT)

(19) Organización de la Propiedad Intelectual Mundial
Oficina Internacional

(43) Fecha de Publicación Internacional
12 de Febrero del 2004 (12.02.2004)



PCT



(10) Número de Publicación Internacional
WO 2004/013156 A1

(51) Clasificación de Patente Inter.: C07J 33/00, A61K 31/58, A61P 11/00

(74) Agente: GRUBB, Philip; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

(21) Número de Solicitud Inter.: PCT/EP2003/008314

(22) Fecha de Presentación Inter.: 28 de Julio del 2003 (28.07.2003)

(25) Idioma de Presentación: Inglés

(26) Idioma de Publicación: Inglés

(30) Datos de Prioridad:
0217504.0 29 de Julio del 2002 (29.07.2002) GB

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

(84) Estados Designados (*regional*): patente Eursiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM). Patente Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR).

(71) Solicitante (*para todos los Estados designados excepto AT, US*): NOVARTIS AG [CH/CH]; Lichstrasse 35, CH-4056 Basel (CH).

Publicada:
- Con Informe de búsqueda internacional

(71) Solicitante (*sólo para AT*): NOVARTIS-PHARMA GMBH [AT/AT]; Brunner Strasse 59, A-1230 Viena (AT).

Para códigos de dos letras y otras abreviaturas, hacer referencia a "Notas de Guía sobre Códigos y Abreviaturas" que aparece al principio de cada emisión regular de la Gaceta del PCT.

(72) Inventores: y
(75) Inventores/Solicitantes: JORDINE, Guido [DE/DE]; Lehener Strasse 148, 79106 Freiburg (DE). MUTZ, Michael [DE/DE]; Mozartstrasse 33, 79104 Freiburg (DE).

(54) Título: POLIMORFISMO DE UN DODECAHIDROCICLOPENTA(A) FENANTRENIL ESTER DEL ACIDO TIOFENCARBOXILICO

(57) Resumen:

Formas de cristal polimórficas de (6S,9R,10S,11S, 13S,16R,17R)-9-cloro-6-fluoro-11-hidroxi-17-metoxycarbonil-10,13,16-trimetil-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahidro-3H-ciclopenta[a]fenantren-17-iléster del ácido 3-metiltiofen-2-carboxílico. Las formas de cristal poseen actividad anti-inflamatoria, y tienen muy buena estabilidad. También se describen métodos para preparar las formas de cristal.

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
12 February 2004 (12.02.2004)

PCT

(10) International Publication Number
WO 2004/013156 A1

- (51) International Patent Classification⁷: C07J 33/00, MUTZ, Michael [DE/DE]; Mozartstrasse 33, 79104
A61K 31/58, A61P 11/00 Freiburg (DE).
- (21) International Application Number: PCT/EP2003/008314 (74) Agent: GRUBB, Philipp; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).
- (22) International Filing Date: 28 July 2003 (28.07.2003) (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SY, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.
- (25) Filing Language: English (84) Designated States (*regional*): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), 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).
- (26) Publication Language: English
- (30) Priority Data: 0217504.0 29 July 2002 (29.07.2002) GB
- (71) Applicant (*for all designated States except AT, US*): NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).
- (71) Applicant (*for AT only*): NOVARTIS PHARMA GMBH ? Published: [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT). — with international search report
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): JORDINE, Guido For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
- [DE/DE]; Lehener Strasse 148, 79106 Freiburg (DE).

(54) Title: POLYMORPHIS OF A KNOWN THIOPHENECARBOXYLIC ACID DODECAHYDROCYCLOPENTA (A) PHENANTHRENYL ESTER

(57) Abstract: Polymorphic crystal forms of 3-methylthiophene-2-carboxylic acid (6S,9R,10S,11S,13S,16R,17R)-9-chloro-6-fluoro-11-hydroxy-17-methoxycarbonyl-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl ester. The crystal forms possess anti-inflammatory activity and have very good stability. Methods for preparing the crystal forms are also described.

WO 2004/013156 A1

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 4-32595A/HO 59	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 03/08314	International filing date (day/month/year) 28/07/2003	(Earliest) Priority Date (day/month/year) 29/07/2002
Applicant NOVARTIS AG		

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

This International Search Report consists of a total of 5 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:

POLYMORPHIS OF A KNOWN THIOPHENECARBOXYLIC ACID DODECAHYDROCYCLOPENTA (A) PHENANTHRENYL ESTER

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

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

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

☐ as suggested by the applicant.

☐ 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 03/08314

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07J33/00 A61K31/58 A61P11/00

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 C07J A61K A61P

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, Y	WO 02 00679 A (NOVARTIS ERFIND VERWALT GMBH; NOVARTIS AG (CH); BEATTIE DAVID (GB)) 3 January 2002 (2002-01-03) cited in the application Abstract; page 26, last paragraph; claims 12,13; page 12, paragraphs 2 and 3.	1-6
Y	HALEBLIAN J ET AL: "PHARMACEUTICAL APPLICATIONS OF POLYMORPHISM" JOURNAL OF PHARMACEUTICAL SCIENCES, AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON, US, vol. 58, no. 8, 1 August 1969 (1969-08-01), pages 911-929, XP002020518 ISSN: 0022-3549 the whole document	1-6

☐ 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

"E" document member of the same patent family

Date of the actual completion of the international search

11 November 2003

Date of mailing of the international search report

27/11/2003

Name and mailing address of the ISA

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

Authorized officer

Weisbrod, T

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 7-8

The vague phrase "substantially as herein described" used in claims 7 and 8 is so unclear (Article 6 PCT) that a meaningful search is impossible for these claims.

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 03/08314

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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
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)

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08314

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0200679	A	03-01-2002	AU 8389101 A	08-01-2002
			BR 0112068 A	01-04-2003
			CA 2412541 A1	03-01-2002
			CN 1439018 T	27-08-2003
			CZ 20024203 A3	16-04-2003
			WO 0200679 A2	03-01-2002
			EP 1299409 A2	09-04-2003
			HU 0300783 A2	28-07-2003
			NO 20026253 A	18-02-2003
			US 2003158163 A1	21-08-2003

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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 4-32595A/HO 59	
International application No. PCT/EP 03/08314	International filing date (day/month/year) 28 July 2003 (28.07.03)
(Earliest) Priority date (day/month/year) 29 July 2002 (29.07.02)	
Title of invention POLYMORPHIS OF A KNOWN THIOPHENECARBOXYLIC ACID DODECAHYDROCYCLOPENTA (A) PHENANTHRENYL ESTER	
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.) Novartis AG Lichtstrasse 35 4056 Basel CH	Telephone No. +4161 324 11 11
	Facsimile No. +4161 322 75 32
	Teleprinter No.
	Applicant's registration No. with the Office
State (that is, country) of nationality: CH	State (that is, country) of residence: CH
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Novartis Pharma GmbH Brunner Strasse 59 1230 Vienna AT	
State (that is, country) of nationality: AT	State (that is, country) of residence: AT
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) JORDINE, Guldo Lehener Strasse 148 79106 Freiburg DE	
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
☒ Further applicants are indicated on a continuation sheet.	

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Sheet No. .2.

International application No.
PCT/EP 03/08314

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.)*

MUTZ, Michael
Mozartstrasse 33
79104 Frelburg
DE

State *(that is, country)* of nationality:
DE

State *(that is, country)* of residence:
DE

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

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

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

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

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.

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43**Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**The 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 name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)GRUBB, Philip
Novartis AG
Corporate Intellectual Property
4002 Basel
CH

Telephone No.

+4161 324 11 11

Facsimile No.

+4161 322 75 32

Teleprinter No.

Agent's registration No. with the Office

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

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

☒ the international application as originally 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 | : | 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).

In the name of the applicants, the representative



16.02.2004

GRUBB, Phillip AV 36671 + 46171

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

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

29.1.05

Applicant's or agent's file reference 4-32595AHO 59		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAA16)	
International application No. PCT/EP 03/08314	International filing date (day/month/year) 28.07.2003	Priority date (day/month/year) 29.07.2002	
International Patent Classification (IPC) or both national classification and IPC C07J33/00			
Applicant NOVARTIS AG et al.			
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 8 sheets, including this cover sheet. ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of 1 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 65.2(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 18.02.2004		Date of completion of this report 15.10.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tlx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Weisbrod, T Telephone No. +49 89 2399-8831 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/08314**

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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

1-12 as originally filed

Claims, Numbers

1-7 filed with telefax on 05.10.2004

Drawings, Sheets

1/1 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:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/08314**

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. 6,7

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):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 6,7 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ 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. 6,7

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	1-5
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-5
Industrial applicability (IA)	Yes: Claims	1-5
	No: Claims	

2. Citations and explanations

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/08314**

see separate sheet

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Re Item I

Basis of the opinion

During the procedure the applicant has filed an amended set of claims. In amended claim 1 reference to crystal form A of compound (I) has been deleted, and original claim 5 (directed to a process for preparing form A of compound I) has been deleted. The amendments comply with the requirements of Article 19(2) and 34(2)(b) PCT.

The application is now directed to

- (i) crystal form B of a thiophenecarboxylic acid cyclopenta[a]hydrophenanthrenyl ester (I) (claim 1),
- (ii) a pharmaceutical composition comprising these crystal forms (claims 2-3),
- (iii) the medical use of these crystal form (claim 4),
- (iv) a method for preparing crystal form B of compound (I) (claim 5), and
- (v) a crystal form (i.e. at least the forms A and B) "substantially as herein described with reference to the examples resp. drawings" (independent claims 6 and 7).

Re Item III

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

The ISA has not issued a search report for claims 6 and 7. No International Preliminary Examination has thus been carried out with regard to novelty and inventive step for subject-matter which is not covered by the search report (cf. Rule 66.1(e) PCT).

Re Item 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 Reference is made to the following documents.

- D1: WO 02/00679 A, 03.01.2002; cited in the application.
- D2: Halebian, J.; McCrone, W. J. *Pharm. Sci.* 1969, 58, 911-929.
- D3: Caira, M. R. in *Topics Curr. Chemistry* 1998, 198, 163-208.

2 Novelty

ST
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D1 discloses the present compound (I) (example 26), the corresponding pharmaceutical composition and its medical use (claims 12, 13; and page 12, paragraphs 2 and 3). In this context, the document describes a method for preparing compound (I) comprising its crystallisation from isopropanol as final process step (page 26, last paragraph). Crystallisation conditions other than the solvent (e.g. concentration or temperature profile) are not reported in D1.

If the claimed product and the known product are identical except for the parameters through which the claimed product is defined, the onus lies with the applicant to substantiate novelty over the product of the prior art. This would also apply if the claimed product was obtained by a process different from that of the prior art. In the present case, however, the application shows already that equilibrating compound (I) at room temperature in methanol, ethanol, and dichloromethane leads to the claimed crystal form B, whereas equilibrating compound (I) at room temperature in isopropanol affords the crystal form A. The different identity of both forms is shown by the XRPD's of the present figures 1 and 2. In view of the experimental results of the present application and the lack of any further crystallisation conditions in D1, it appears justified to conclude that the procedure of D1 affords compound (I) in the crystal form A, whereas the present claims 1-5 relate to the crystal form B. Hence, the present claims 1-5 appear novel vis-à-vis D1.

D2 and D3 relates to polymorphism of organic compounds. The documents are not relevant to the question of novelty of the application, because compound (I) is not disclosed therein.

3 Inventive Step

3.1 The application describes the preparation and characterisation of the crystal forms A and B of compound (I), which are useful in treating antiinflammatory conditions. Furthermore, the application states that some ("of the two") crystal forms have very good stability, facilitating their use in the preparation of pharmaceutical dosage forms (the application, page 1).

3.2 D1 discloses compound (I) (crystallised from isopropanol and considered to represent the present crystal form A) as an inhibitor of TNF-alpha synthesis and its use in the manufacture of a medicament for the treatment of an inflammatory condition. D1 is thus considered to represent the most relevant state of the art.

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/08314

According to the experimental results presently on file the claimed crystal form B differs from form A of D1 through certain physicochemical parameters (which is to be expected for polymorphs). In view of D1 the problem underlying the application is seen in the provision of a further crystal form of compound (I) useful for the preparation of pharmaceutical dosage forms for the same therapeutic application.

Since the pharmaceutical effect of a pharmaceutical active ingredient (in the present case the antiinflammatory activity of the present compound I) is based on its molecular structure rather than on its solid state properties, the present claimed crystal form B of compound (I) is merely an obvious alternative of the crystal form of D1 for the same therapeutic application. In the absence of any substantiated unexpected effect relevant for the therapeutic application or the processing of the claimed crystal form B in comparison with the crystal form A of D1, no inventive step would be acknowledged for the claimed crystal form and subject matter referring to this crystal form. Consequently, the present claims 1-5 do, at present, not involve an inventive step.

In this context the applicant is reminded that according to the common general knowledge of a person skilled in the art most substances when investigated for a sufficiently long time reveal more than one polymorph. Furthermore, in the pharmaceutical industry the systematic investigation of polymorphism is routine practice (cf. D3, page 165, last paragraph to page 166, first paragraph). Mere different properties concerning the solubility, bioavailability, density, melting point, or chemical reactivity of the claimed crystal form in comparison with the corresponding properties of the known crystal form would be insufficient to establish an inventive step, because such different properties can be readily expected by the person skilled in the art (cf. e.g. D2; or D3, page 164, paragraph 1; and page 165, paragraph 2). The diffraction pattern and the melting point with simultaneous decomposition of the claimed crystal form B (with melting and decomposition occurring at 270 °C compared to 264 °C for form A) does not appear relevant for its therapeutic application or processing and, is therefore unsuited to establish an inventive step. Equally, the unpredictability of the diffraction pattern and melting point of a new polymorph is irrelevant for the assessment of inventive step.

- 3.3 If the applicant, however, would submit that the problem underlying the application was the provision of an improved i.e. thermodynamically more stable crystal form of compound (I), then it is noted that at present no argument has been provided that the claimed crystal form B is in fact thermodynamically more stable than the

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crystal form A of D1. Under these circumstances, the only basis for accepting that the claimed crystal form would solve the problem posed (i.e. being thermodynamically more stable), would be common general knowledge. The same common general knowledge, however, would be similarly applicable to the assessment whether the solution of the technical problem is to be considered obvious. Hence, in the absence of any substantiation of the technical effect and any instructions how said effect has been assessed, no inventive step would be acknowledged for the claimed matter.

In this context it is furthermore noted that from the higher melting point of the crystal form B alone (without knowing the interrelationship of the crystal forms A and B), it cannot be concluded that the crystal form B would be thermodynamically more stable than the crystal form A, because only in monotropic polymorphic systems the high melting form is at all temperatures thermodynamically more stable than the low melting form. In enantiotropic systems, however, the low melting polymorph is the thermodynamically stable form below the transition temperature, whereas the high melting form is the thermodynamically stable one above the transition temperature. Consequently, it is at present not evident whether the claimed or the known crystal form of compound (I) is the thermodynamically stable one and at which temperature.

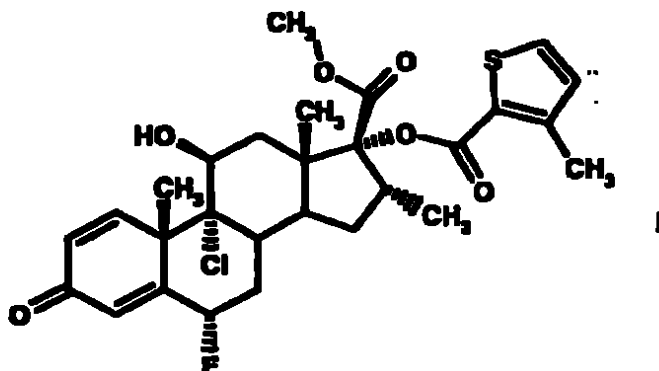
4 Deficiencies of the Application under Article 6 PCT

Claims 7 and 8 are to be objected under Article 6 in combination with Rule 6.2(a) PCT for referring to the description. In addition the vague phrase "substantially as herein described" renders the claims incomprehensible.

4-32595P1/ HO 59 PCT

CLAIMS

1. A compound of formula I



in a crystal form B that has a melting point, by Differential Scanning Calorimetry, of about 270°C with simultaneous decomposition, at a heating rate of 20° C/min and the following characteristic diffraction lines (2θ in angular degrees ± 0.2°) in the X-ray diffraction pattern thereof: 7.2°, 9.3°, 12.0°, 12.8°, 13.1°, 14.5°, 17.4°, 20.4°, 23.2° and 25.8°.

2. A pharmaceutical composition comprising, as active ingredient, an effective amount of the compound of formula I in crystal form B as defined in claim 1, optionally together with a pharmaceutically acceptable carrier.

3. A composition according to claim 2, which is in inhalable form.

4. The use of a compound according to claim 1 in crystal form B for the preparation of a medicament for the treatment of an inflammatory or obstructive airways disease.

5. A method of preparing a compound of formula I in crystal form B as defined in claim 1 which comprises crystallising the compound of formula I as defined in claim 1 from a solution thereof in ethanol, methanol or methylene chloride.

6. A crystal form of the compound of formula I, substantially as herein described with reference to any of the Examples.

7. A crystal form of the compound of formula I, substantially as herein described with reference to either of the drawings.

PATENT COOPERATION TREATY

Corporate Intellectual Property

10. Mai 2004

F/F M/D F/L PS Copy

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GRUBB, Philip
Novartis AG
Corporate Intellectual Property
CH-4002 Basel
SUISSE

PCT 11 MAY 2004

WRITTEN OPINION
(PCT Rule 66)Date of mailing
(day/month/year)

06.05.2004

Applicant's or agent's file reference
4-32595AHO 59

REPLY DUE

within 3 month(s)
from the above date of mailingInternational application No.
PCT/EP 03/08314International filing date (day/month/year)
28.07.2003Priority date (day/month/year)
29.07.2002International Patent Classification (IPC) or both national classification and IPC
C07J33/00, C07J33/00Applicant
NOVARTIS AG et al.

1. This written opinion is the second drawn up by this International Preliminary Examining Authority.
2. 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
3. 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 66.5 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 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 29.11.2004

Name and mailing address of the international
preliminary examining authority:European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523858 apmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Weisbrod, T

Formalities officer (incl. extension of time limits)
Hebert, W
Telephone No. +49 89 2399-2152

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WRITTEN OPINION

International application No. PCT/EP 03/08314

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

1-12 as originally filed

Claims, Numbers

1-8 as originally filed

Drawings, Sheets

1/1 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:

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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:

☐ the entire international application,

☒ claims Nos. 7-8

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):

☐ 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. 7-8

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 1-5

Inventive step (IS) Claims 1-6

Industrial applicability (IA) Claims

2. Citations and explanations

see separate sheet

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**WRITTEN OPINION
SEPARATE SHEET**

International application No. PCT/EP03/08314

Re Item I

Basis of the opinion

The application is directed to

- (i) crystal forms A and B of a thiophenecarboxylic acid cyclopenta[a]hydrophenanthrenyl ester (I) (claim 1),
- (ii) a pharmaceutical composition comprising these crystal forms (claims 1-2),
- (iii) the medical use of these crystal forms (claim 4),
- (iv) a method for preparing crystal form A of compound (I) (claim 5),
- (v) a method for preparing crystal form B of compound (I) (claim 6), and
- (vi) the said crystal forms "substantially as herein described with reference to the examples resp. drawings" (independent claims 7 and 8).

Re Item III

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

The ISA has not issued a search report for the claims 7 and 8 (cf. search report). No International Preliminary Examination will thus be carried out with regard to novelty and inventive step for subject-matter which is not covered by the search report (cf. Rule 66.1(e) PCT).

Re Item 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 Reference is made to the following documents. D3 has not been cited in the search report; a copy is thus annexed to this communication.

D1: WO 02/00679 A, 03.01.2002; cited in the application.

D2: Haleblan, J.; McCrone, W. *J. Pharm. Sci.* **1969**, *58*, 911-929.

D3: Caira, M. R. in *Topics Curr. Chemistry* **1998**, *198*, 163-208.

2 Novelty

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Claims 1-5 do not comply with the criterion of novelty (Article 33(2) PCT).

D1 discloses the present compound (I) (example 26), the corresponding pharmaceutical composition and its medical use (claims 12, 13; and page 12, paragraphs 2 and 3), as well as a method for its preparation comprising crystallising the compound (I) from isopropanol (page 26, last paragraph) as claimed in present claim 5. Although, the melting point and X-ray diffraction pattern of compound (I) is not disclosed in D1, the claimed crystal forms A and B as well as the subject matter of the claims 2-5 are considered to lack novelty in view of D1, unless the applicant was able to provide substantiated evidence (by appropriate comparison tests) that the claimed crystal forms are in fact different from the material disclosed in D1 (cf. page 26, last paragraph). Present claim 6 is considered novel vis-à-vis D1, because a method for preparing compound (I) comprising its crystallisation from ethanol, methanol or methylene chloride is not disclosed in the prior art document.

D2 and D3 relates to polymorphism of organic compounds. The documents are not relevant to the question of novelty of the application, because compound (I) is not disclosed therein.

3 Inventive Step and Unity of Invention

In view of the novelty objection raised above a detailed assessment of inventive step for possibly novel subject matter is at present not applicable. If the applicant, however, was able to establish novelty for one or both of the claimed crystal forms the following observation, most probably, would apply to the requirements of inventive step.

- 3.1 The application describes the preparation and characterisation of the crystal forms A and B of compound (I), which are useful in treating antiinflammatory conditions alike the compound (I) of D1. Furthermore, the application states that some ("of the two") crystal forms have very good stability, facilitating their use in the preparation of pharmaceutical dosage forms (the application, page 1).
- 3.2 D1 discloses already compound (I) (crystallised from isopropanol) as an inhibitor of TNF-alpha synthesis and its use in the manufacture of a medicament for the

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treatment of an inflammatory condition. If one or both of the claimed crystal forms were novel over the compound (I) of D1, the main problem underlying the application starting from D1 would be seen in the provision of further solid form(s) of example 26 of D1 which are useful for the preparation of pharmaceutical dosage forms. Since the pharmaceutical effect of a pharmaceutical active ingredient (in the present case the antiinflammatory activity of the present compound I) is based on its molecular structure rather than on its solid state properties, the present claimed crystal forms of compound (I) are merely obvious alternatives of the crystal form of D1 for the same therapeutic application. No inventive step would thus be acknowledged for one or two mere novel crystal form(s) of compound (I), unless the applicant was able to substantiate an unexpected property (for one novel crystal form) respectively a common unexpected property (for two novel crystal forms) of the claimed crystal form(s) in comparison with the known crystal form according to example 26 of D1. In this context the applicant is reminded that according to the common general knowledge of a person skilled in the art most substances when investigated for a sufficiently long time reveal more than one polymorph and the systematic investigation of polymorphism is routine practice in the pharmaceutical industries (cf. D3, page 165, last paragraph to page 166, first paragraph). Furthermore, mere different properties concerning the solubility, bioavailability, density, melting point, or chemical reactivity of the claimed crystal form in comparison with the corresponding properties of the known crystal form would be insufficient to establish an inventive step, because such different properties can be readily expected by the person skilled in the art (cf. e.g. D2; or D3, page 164, paragraph 1; and page 165, paragraph 2).

3.3 In this context it is also noted that for the requirement of unity to be met the subject-matter (e.g. the claimed crystal forms A and B) should be characterized by a common distinguishing feature over the prior art. If the applicant was able to substantiate novelty for only one of the claimed polymorphs (e.g. form B; whereas form A and the form of D1 were identical), then, there was a lack of unity among the claims directed or relating to the novel crystal form and the claim relating to a method for preparing the known crystal form.

4 Deficiencies of the Application under Article 6 PCT

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**WRITTEN OPINION
SEPARATE SHEET**

International application No. PCT/EP03/08314

Claims 7 and 8 are to be objected under Article 6 in combination with Rule 6.2(a) PCT for referring to the description. In addition the vague phrase "substantially as herein described" renders the claims incomprehensible.

Amendments

The applicant's attention is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed (Article 19(2) and 34(2)(b) PCT). When filing new claims, the complete set of claims should be filed rather than single amended sheets. Additionally, one set indicating the amendments in hand-writing should be provided. The applicant, furthermore, should clearly indicate the location of those places in the original application which would support each of the specific amendments.

10. März 2004

F/F M/D F/L PS. Copy

PCT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GRUBB, Philip
Novartis AG
Corporate Intellectual Property
CH-4002 Basel
SUISSE

WRITTEN OPINION

(PCT Rule 66)

11 MAR 2004

Reg. Letter

Date of mailing
(day/month/year) 08/03/2004

Applicant's or agent's file reference
4-32595A/HO 59

REPLY DUE
within 2 / 00 months/days
from the above date of mailing.

International application No.

PCT/EP03/08314

International filing date (day/month/year)

28/07/2003

Priority date (day/month/year)

29/07/2002

International Patent Classification (IPC) or both national classification and IPC

C07J33/00

Applicant

NOVARTIS AG et al.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. 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

3. 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 66.4bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 29/11/2004

Name and mailing address of the IPEA/



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Authorized officer

Examiner

Formalities officer
(incl. extension of time limits)
Tel. (+49-89) 2399 2828



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I. Basis of the opinion

The basis of this written opinion is the application as originally filed.

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

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

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

1. To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:
2. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).
3. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.



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Germany

Fax no. 00 49 89 2399 4465
Number of pages 1 including this page

Date 21 April 2004

Concerning International patent application PCT/EP03/08314
Novartis AG Case 4-32595A/HO 59

Dear Sirs,

I refer to the Written Opinion issued under Rule 66 PCT dated 8 March 2004 and hereby request detailed International Preliminary Examination.

I also request that the Examiner issues a second written opinion instead of establishing an international preliminary examination report directly.

Yours faithfully

Bernard A Marsh
GA 36671

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Craig S McLean
Patent Specialist, Respiratory
European Patent Attorney

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Germany

Fax no. 00 49 89 2399 4465
Number of pages 6 including this page

Date 5 October 2004

Concerning International patent application PCT/EP03/08314 – Deadline 6 October 2004
Novartis AG Case 4-32595A/HO 59

Dear Sirs,

I refer to the second Written Opinion issued under R66.2 PCT dated 6 May 2004 and the communication dated 1 August 2004 extending the time limit for replying to that.

Amendments

The applicant wishes to amend the claims as outlined in the worksheet of amendments enclosed herewith. Replacement pages are also enclosed.

Novelty

The Examiner has objected that claims 1 to 5 lack novelty within the meaning of Article 33(2) PCT over D1 (WO 02/00679). Claims 1-4 have been amended to refer to crystal form B only and Claim 5 has been deleted.

D1 discloses 3-methylthiophene-2-carboxylic acid (6S,9R,10S,11S,13S,16R,17R)-9-chloro-6-fluoro-11-hydroxy-17-methoxycarbonyl-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl ester (herein the "Steroid"), which is a corticosteroid that possesses a high anti-inflammatory activity. A method for preparing this compound is disclosed in Example 26.

The Examiner acknowledges D1 does not explicitly disclose a crystal form of the Steroid that has the claimed melting point or X ray diffraction pattern of crystal form B. However the Examiner objects that D1 implicitly discloses the claimed crystal form.

The method given in D1 for preparing the Steroid involves hydrochlorinating 3-methylthiophene-2-carboxylic acid (6S,9S,10S,11S,13S,16R,17R)-9,11-epoxy-6-fluoro-17-methoxycarbonyl-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-

3H-cyclopenta[a]phenanthren-17-yl ester in toluene, evaporating that solvent to give a crude product. That crude product is crystallised firstly from acetonitrile and secondly from isopropanol to afford the Steroid. It appears the crystal form of this product is in fact crystal form A, which is no longer claimed. Crystal form B has a different melting point, a different diffraction pattern and is not produced by that method. Claims 1 to 4, which now only refer to crystal form B, are therefore novel over D1.

The Examiner has already acknowledged that claim 6 (now claim 5) to the method for preparing crystal form B is novel over D1.

Inventive step over D1 when combined with D2 or D3

The Examiner has not made a detailed assessment of inventive step however the Applicant submits there is nothing in D1 that would allow one of ordinary skill in the art to predict that the Steroid would have crystal form B as characterised by the claimed melting point and X-ray diffraction pattern.

The technical problem that is addressed by the present invention can be expressed as the provision of a crystal form of the Steroid that is thermodynamically stable and thus suitable for use in formulating a commercial pharmaceutical product.

It is common in the pharmaceutical industry to investigate polymorphisms when developing an active ingredient into a safe and effective pharmaceutical product. It is critical that the active ingredient contained in that product is present in a thermodynamically stable form. This means there is often a need to investigate polymorphisms. It could be said such investigations are routinely carried out, however it does not follow that the solving those problems is a routine exercise for one of ordinary skill in the art and does not require any inventive capacity. D3 (Caira et al, Topics Curr. Chem. 1998) illustrates the wide range of thermodynamic, kinetic and structural issues concerned with polymorphisms and the variety of techniques that are used to investigate these in order to solve these problems. It also highlights there are many unanswered questions and gaps in understanding how polymorphism occurs and how different polymorphic forms affect the manufacture and properties of novel pharmaceutical chemical compounds.

There is nothing in D3 that would have enabled one of ordinary skill in the art to predict before the priority date that the Steroid would have a crystal form with the claimed melting point and diffraction pattern.

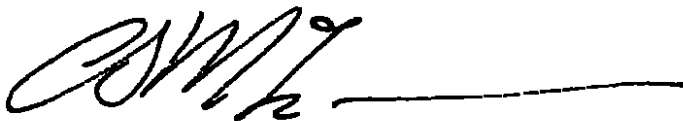
D2 (Haleblian et al J. Pharm. Sci. 1969) reviews many of the same issues associated with investigating polymorphisms and the various methods for studying these. However, like D3, there is simply nothing in D3 that would have enabled one of ordinary skill in the art to predict before the priority date that the Steroid would have a crystal form with the claimed melting point and diffraction pattern.

In view of the above, the Applicant submits the claims meet the requirements of Article 33(3) PCT.

Deficiencies under Article 6 PCT

The Examiner's comments with regard to Claims 7 and 8 (now claims 6 and 7) are noted. It is appreciated that the omnibus claim format is not allowable in all jurisdictions.

Yours faithfully

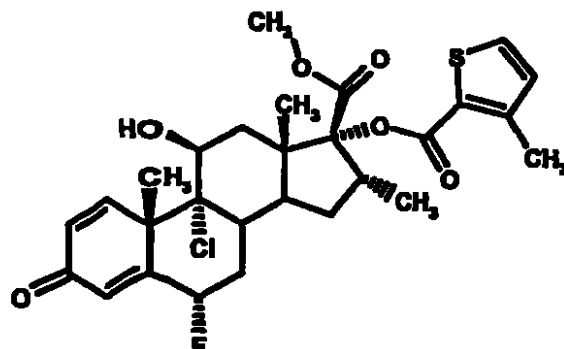
A handwritten signature in black ink, appearing to read 'CSM', followed by a horizontal line.

Craig S McLean
GA 36671

Enc Worksheet of amendments (2 pages)
Replacement page (1 page)

CLAIMS

1. A compound of formula I



~~in a crystal form A that has a melting point, by Differential Scanning Calorimetry, of about 264°C with simultaneous decomposition, at a heating rate of 20° C/min and the following characteristic diffraction lines (2θ in angular degrees ± 0.2°) in the X-ray diffraction pattern thereof: 3.6°, 7.3°, 13.4°, 14.6°, 16.3°, 22.0°, 25.8°, 25.9°, 29.5°, or~~

in a crystal form B that has a melting point, by Differential Scanning Calorimetry, of about 270°C with simultaneous decomposition, at a heating rate of 20° C/min and the following characteristic diffraction lines (2θ in angular degrees ± 0.2°) in the X-ray diffraction pattern thereof: 7.2°, 9.3°, 12.0°, 12.8°, 13.1°, 14.5°, 17.4°, 20.4°, 23.2° and 25.8°.

2. A pharmaceutical composition comprising, as active ingredient, an effective amount of the compound of formula I in crystal form ~~A~~ or B as defined in claim 1, optionally together with a pharmaceutically acceptable carrier.

3. A composition according to claim 2, which is in inhalable form.

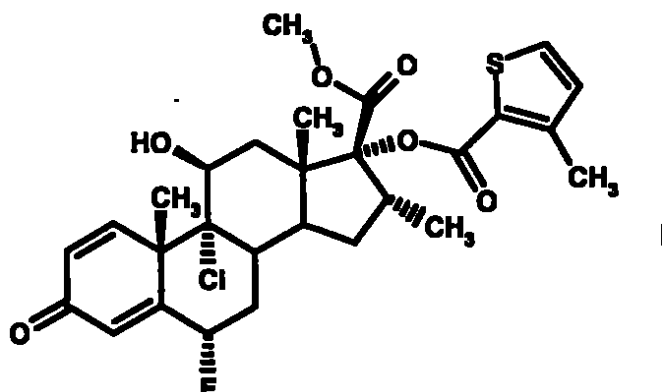
4. The use of a compound according to claim 1 in crystal form ~~A~~ or B for the preparation of a medicament for the treatment of an inflammatory or obstructive airways disease.

~~5. A method of preparing a compound of formula I in crystal form A as defined in claim 1 which comprises crystallising the compound of formula I as defined in claim 1 from a solution thereof in isopropanol, ethyl acetate, n-butanol, hexane, heptane, tert-butylmethylether, toluene or tetrahydrofuran.~~

- ~~5~~ 6. A method of preparing a compound of formula I in crystal form B as defined in claim 1 which comprises crystallising the compound of formula I as defined in claim 1 from a solution thereof in ethanol, methanol or methylene chloride.
- ~~6~~ 7. A crystal form of the compound of formula I, substantially as herein described with reference to any of the Examples.
- ~~7~~ 8. A crystal form of the compound of formula I, substantially as herein described with reference to either of the drawings.

CLAIMS

1. A compound of formula I



in a crystal form B that has a melting point, by Differential Scanning Calorimetry, of about 270°C with simultaneous decomposition, at a heating rate of 20° C/min and the following characteristic diffraction lines (2θ in angular degrees ± 0.2°) in the X-ray diffraction pattern thereof: 7.2°, 9.3°, 12.0°, 12.8°, 13.1°, 14.5°, 17.4°, 20.4°, 23.2° and 25.8°.

2. A pharmaceutical composition comprising, as active ingredient, an effective amount of the compound of formula I in crystal form B as defined in claim 1, optionally together with a pharmaceutically acceptable carrier.

3. A composition according to claim 2, which is in inhalable form.

4. The use of a compound according to claim 1 in crystal form B for the preparation of a medicament for the treatment of an inflammatory or obstructive airways disease.

5. A method of preparing a compound of formula I in crystal form B as defined in claim 1 which comprises crystallising the compound of formula I as defined in claim 1 from a solution thereof in ethanol, methanol or methylene chloride.

6. A crystal form of the compound of formula I, substantially as herein described with reference to any of the Examples.

7. A crystal form of the compound of formula I, substantially as herein described with reference to either of the drawings.



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Number of pages 1 including this page

Date 4 August 2004

Concerning International patent application PCT/EP03/08314
Novartis AG Case 4-32595A/HO 59

Dear Sirs,

I refer to the Written Opinion issued under Rule 66 PCT dated 6 May 2004 and hereby request to extend the time limit for replying to this by two months under Rule 66.2(d) PCT.

Yours faithfully

Craig S McLean
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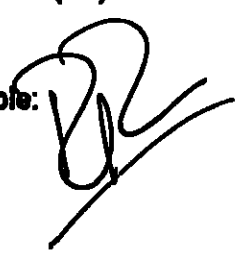
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SUPERINDUSTRIA Y COMERCIO

Radicacion : 03010470 00000000 Folios: 73
Fecha (AMD): 2005-02-07 15:51:35
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 0020 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:

INFORME DE PROTOCOLO

Expediente 05 - 10470 .

Fecha: 21 de febrero de 2005 .

Se certifica que:

Desde fecha 16 de Abril de 1997 ,
del folio 90.643 al folio 90.650 del
libro de Protocolo NI 311 , obra el
poder NI 17398 conferido por NOVARTIS AG
(NOVARTIS SA) (NOVARTIS INC)
domiciliado(a) en Basilea, Suiza al doctor
Jimena Escobar Uribe y/o Ignacio Escobar Uribe
_____ .

Facultad para desistir y sustituir si .

Revisado 202027 .

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2020
Bogotá, D.C.,

Doctor(a)
JIMENA ESCOBAR URIBE

Oficio N° 12377

ASUNTO:	Radicación N°	05-10470
	Solicitud internacional	PCT/EP2003/008314
	Fecha inicio fase nacional	28/02/2005
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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

- La sociedad solicitante en fase nacional difiere de la publicada con la solicitud internacional, por lo tanto debe aclarar, o adecuar los documentos para tal fin.

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 11 MAR 2005.

202027

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