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Delegatura de propiedad Industrial

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PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 06-19204

54. **TÍTULO** *PROCESO DE PURIFICACION*

51. **CLASIFICACIÓN INTERNACIONAL** C07C 209/084

71. **SOLICITANTE(N)** *NOVARTIS AG*

DOMICILIO *BASILEA, SUIZA*

74. **APODERADO** *JIMENA ESCOBAR URIBE*

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
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1 SOLICITUD DE:

[X] Patente de Invención [ ] Patente de Modelo de Utilidad

[ ] Capitulo I [X] Capitulo II

2 SOLICITANTE: (71)	Nombre: **NOVARTIS AG** Dirección: Lichtstrasse 35 CH-4002 Basilea, Suiza Nacionalidad o Domicilio: Basilea, Suiza Lugar de Constitución Suiza Teléfono: 41613241111 Fax: 41613227532 E-mail	**IDENTIFICACIÓN** C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] **Número**
3 REPRESENTANTE O APODERADO (74)	Nombre: JIMENA ESCOBAR URIBE Dirección: Cra. 11A No. 94-76 (Of. 305) Teléfono: 6 162051/61 Fax: 6 161889 E-mail: tm-patent@escobaruribe.com	**IDENTIFICACIÓN** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] **Número** 39.779.452T.P 68228
4 INVENTOR (ES) (72)	Nombre: **VER ANEXOS** Dirección: Nacionalidad o domicilio:	

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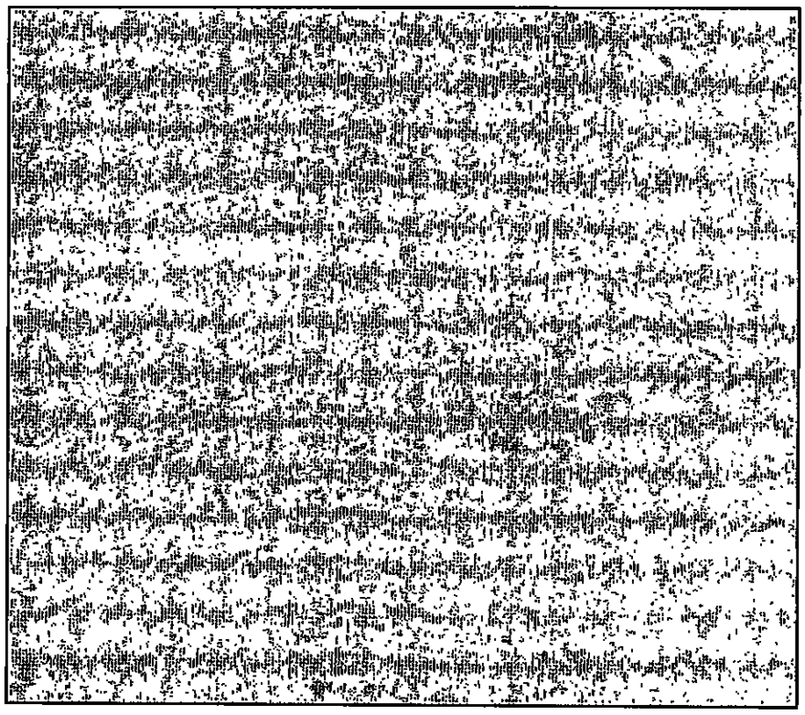
10 ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica No. 17.398
- [x] Poderes si fuere el caso * **Protocolo No. 17.398**
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] 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
- [x] Otros "Opinión escrita".

11 FIGURA CARACTERÍSTICA



12 Solicito la concesión de la patente

NOMBRE JIMENA ESCOBAR URIBE

FIRMA

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CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
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ANEXOS

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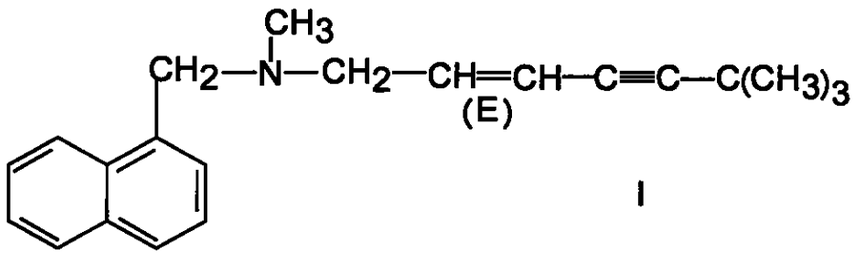
Solicito expresamente a nombre de la sociedad **NOVARTIS AG**, sociedad constituida de conformidad con las leyes de Suiza, domiciliada en Lichtstrasse 35, CH-4056 Basilea, Suiza, el otorgamiento de Patente para la invención titulada **"PROCESO DE PURIFICACION".**

Clase: C07C 209/84

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

RESUMEN:

PROCESO DE PURIFICACION

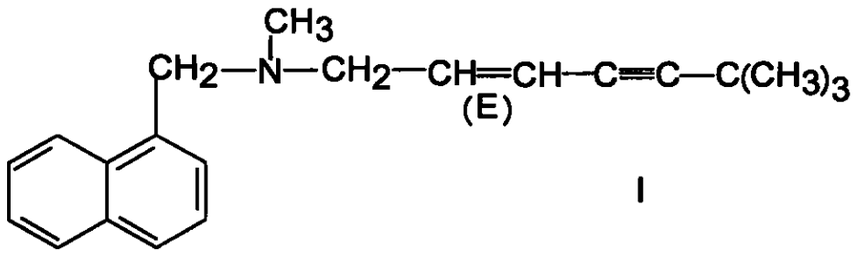


I

Proceso de purificación para la preparación de alilamina terbinafina farmacéutica de formula (I), en la forma de base libre o en la forma de la sal por adición de acido, por destilación de la terbinafina base cruda, preferiblemente por destilación de camino corto, e.g., a una temperatura por encima de 100°C y a presión reducida. E.g., 0.2 mbar, y recuperación del producto purificado en la forma de base libre o de sal por adición de acido.

contra hongos del p lvo y dimórficos, y contra algunas levaduras patógenas del genero *Pityrosporum, Candida y Rhodotorula.*

La estructura de la terbinafina es como se muestra en la fórmula I



I

Y su nombre químico es i.a.

(E)-N-(6,6-dimetil-2-hepten-4-inil)-N-metil-1-naftaleno metanamina.

Esta puede estar en la forma de base libre o en la forma de la sal de adición ácida. La forma de la sal de adición ácida se puede preparar a partir de la base libre de una manera convencional y viceversa. Ejemplos adecuados de formas de sales de adición ácida son el clorhidrato, el lactato, el ascorbato y el malato, e.g. L-(-)-hidrogenmalato. Se prefieren la base libre y el clorhidrato y las sales clorhidrato y malato. Como se aprecia en la fórmula I anterior la terbinafina es un compuesto alilamina con un enlace triple conjugado con un doble enlace en la cadena lateral. La terbinafina se inventó hace varios años (ver e.g. EP24587, Ejemplo 16) y tal estructura eno-ino conjugadas fue, y aún es, altamente inusual en el campo farmacéutico, constituyendo una característica estructural novedosa en la química medica.

Ambos, el doble y el triple enlace usualmente son altamente reactivos. Aunque la literatura química no excluye que compuestos con tal estructura puedan ser estables, algunos son inestables y se pueden descomponer bajo almacenamiento o

por procesamiento, como cuando se aplica calor, e.g. por destilación a temperaturas elevadas.

Así parece de e.g. E.R.H. Jones et al., J. Chem. Soc. (1960) 341-346 ya que al someter el penta-1,2dien-4-ino puro a destilación simple a su temperatura de ebullición normal de 57^0, se descompone. Similarmente el dímero (no conjugado) 1-2 alquen-4-ino [CH_2=CH-CH_2-C=C-$C(CH_3)(OH)$-]$_2$, i.e. 6,7dimetil –dodeca-1,11-dieno-4,8-diino-6,7diol (compuesto V en H. Disselnkotter y P. Kurtz, Ann. Chem [1964] 26-34 produce descomposición considerable por destilación a una temperatura baja (85-90^0C y una presión 0.05 mm Hg) así como también por nueva destilación entre 81-85^0C y 0.03 mm Hg. Además, el eno-diino (Z,Z)-3,7-decadieno-1,5,9 triino polimeriza rápidamente cuando se termoliza puro y en solución a 170-190^0C para dar naftaleno, mientras que la termólisis de los isómeros correspondientes (E,Z) y (E,E) dan otros productos o un polímero (J. Am. Chem. Soc. 114 [1992] 3120 – 3121).

Además la isomerización de compuestos eno-ino conjugados, e.g. del éter CH_3CH = CH-C=C-$CH_2OC_2H_5$ al correspondiente compuesto 1,3,5-trieno puede estar acompañado por considerables residuos poliméricos después de la destilación que resultan de la eliminación acompañante 1,6 del etanol, mientras que el reemplazo del grupo –OC_2H_5 con un grupo amino produce una aromatización (Van-Dongen, J. et al., Recueil Trav. Chim. Pays-Bas 86 [1967] 1077-1081).

Adicionalmente, sobre todo, notablemente, parece e.g. de las publicaciones anteriores que cuando la destilación se afecta en todo con los derivados eno-ino, esta usualmente se afecta a temperaturas por debajo o ligeramente por encima de 100^0C, especialmente por debajo de cerca de 125^0C, como se espera con compuestos altamente reactivos susceptibles de descomposición o degradación o polimerización, o a una explosión por calentamiento. Esto ocurre también para la mayoría de los

derivados alquen-ino divulgados en e.g. Recueil Trav. Chim. Pays-Bas 85 (1966) 952-965 y Zh. Org. Khim. 3 (1967) 1792-3 (CA 68 [1968] 12370), mientras que los dos intermedios para feromonas divulgados en Czech Autor's Certificate No. 232843 (CA 106 [1984] 213632b) se purifican por destilación a presión reducida a 102-115°C y 118-125°C, respectivamente.

Además, la terbinafina en la forma de base libre ebulle a 140°C a 0.3 mbar de presión, y a esta temperatura su estabilidad térmica es limitada: por lo tanto se puede observar la siguiente descomposición térmica (según análisis por cromatografía de gases; el área bajo el pico de un compuesto relativo a la suma de todos los picos se denomina área-porcentaje; en el caso del isómero Z, el área-porcentaje debería ser aproximadamente idéntica con el porcentaje en peso):

Tiempo de calentamiento (h)	**Para el producto 1 (Área-%)**	**Isómero-Z (Área-%)**	**Isómero-E no cambiado (Área-%)**
0	0.09	0.25	97.6
7	0.57	0.34	96.6
23	0.92	0.45	94.7
32	1.20	0.52	92.0

Para el producto 1 = (metil) (naftalen-1-ilmetil)amina

De otro lado el producto solidifica por debajo de 43°C.

Por lo tanto uno normalmente refrenaría las operaciones efectivas que requieren aplicación sustancial de calor cuando se trabaja un compuesto químico con tal estructura inusual, y particularmente cuando ésta se asocia con una estabilidad térmica limitada, especialmente en operaciones a gran escala, tal como es en la producción industrial farmacéutica. Por ejemplo, en el Ejemplo 13 de Banyu EP 0

421302 A2 que describe una preparación de terbinafina, la mezcla cruda (base libre) obtenida después de la reacción se somete a purificación por cromatografía en silicagel.

Sin embargo, se encontró que sorpresivamente y contra-intuitivamente que la terbinafina base se puede someter a destilación sin ningún efecto particularmente desfavorable. Además, se ha encontrado que tal destilación se puede efectuar a temperaturas elevadas, e.g. aún a una temperatura significativamente más alta de 100°C, e.g. de cerca de 110°C a cerca de 170°C, preferiblemente de cerca de 125°C a cerca de 165°C, especialmente de cerca de 160°C, y bajo presión reducida correspondientemente, e.g. 0.2 mbar a 160°C (temperatura de la camisa).

Por lo tanto el rendimiento relacionado es normalmente de cerca del 95%, comenzando del producto crudo.

Además, también se encontró que tal destilación puede ser aún efectiva utilizando grandes cantidades de terbinafina base cruda, i.e. en una cantidad industrial, e.g. en producción a gran escala o terbinafina base purificada y sales por adición de ácidos, e.g. en cantidades de por lo menos cerca de 5 Kg, preferiblemente por lo menos cerca de 50 Kg, especialmente por lo menos cerca de 200 Kg, e.g. de cerca de 500 Kg a cerca de 2 tons, mas preferiblemente de cerca de 600 Kg a cerca de 900 Kg, aún mas preferiblemente de cerca de 800 Kg a cerca de 900 Kg, especialmente de cerca de 850 Kg de producto purificado en la forma de base libre por destilación por lote o corrida.

La invención por lo tanto concierne a un proceso novedoso para la purificación de terbinafina que comprende someter la terbinafina cruda en la forma de base libre a destilación y recoger el producto resultante en la forma de base libre o en la forma de

sal por adición de ácido, de aquí en adelante nombrado abreviadamente **"el proceso de la invención"**.

El proceso de la invención es particularmente útil para separar la terbinafina de sus contaminantes, e.g. contaminantes metálicos resultantes de su síntesis química, e.g. de los catalizadores, tales como cobre y/o en particular, contaminantes de paladio, particularmente para reducir o eliminar contaminantes que resultan de la síntesis de acuerdo con o similarmente al proceso descrito en e.g. Banyu EP 421302 y/o Dipharma EP 1`236`709, e.g. por reacción de (E)-N-(3-halo-2-propenil)-N-metil-N-(1-naftilmetil)amina (compuesto de fórmula IV de EP 421302 en donde R^{11} es metil, R^{21} es 1-naftilmetil y W es halógeno, e.g. bromo, preferiblemente cloro), con 3,3-dimetil-1-butino (compuesto de fórmula V de la misma, en donde R^7 es ter-butilo) en presencia de un catalizador de paladio y/o cobre para obtener terbinafina base. El catalizador es e.g. yoduro de cobre (I), o yoduro de cobre (I) junto con bicloruro de bis-(trifenilfosfina) paladio-(II) o tetrakis (trifenilfosfina) paladio u otro catalizador que contenga paladio-, cobre- o paladio/cobre- seleccionado de aquellos divulgados en EP 421302 A2, e.g. en la página 7, línea 54 a la página 8 línea 18.

El proceso de la invención se puede efectuar por medios convencionales. Preferiblemente se efectúa por un proceso de destilación llamado "suave". Este se puede efectuar e.g. como una destilación por lotes, o preferiblemente de manera continua o semi-continua, y especialmente como una destilación de **"camino corto"**, por lo que el camino entre el manto de calentamiento y el condensador es corto, e.g. del orden de 10 cm, minimizando así el tiempo durante el cual la terbinafina esta a una temperatura elevada, e.g. por encima de 100^0C.

El término "destilación de camino corto" será entendido aquí como una destilación a alto vacío para separar mezclas de compuestos orgánicos (o de silicio)

que no tolerarán calentamientos prolongados sin cambio estructural excesivo o descomposición. Este utiliza el calentamiento de la condensación como un primer cuerpo para irradiar la emisión de calor a la película de la superficie del evaporador. El camino entre el evaporador y el condensador no se obstruye. Con tiempos de residencia cortos y temperaturas de destilación bajas se reduce grandemente el daño térmico a los materiales orgánicos.

El proceso de la invención que utiliza una destilación de camino corto se puede efectuar utilizando aparatos disponibles comercialmente, e.g. como los comercializados por UIC GmbH, D-63755- Alzenau-Horstein, Germany. Un conjunto conveniente es e.g. el que se ilustra en la **figura**.

Se prefiere la destilación de camino corto. Esta permite un tiempo corto de calentamiento de la mezcla que se intenta purificar, así como también un procesamiento cíclico, con las mejoras correspondientes el rendimiento del producto purificado. Además, se reducen el espesor del material sobre la pared del evaporador, permitiendo temperaturas bajas de evaporación y tiempos cortos de residencia. Por lo tanto se alcanza una muy eficiente separación de los contaminantes, sin necesidad de otras etapas de purificación tales como cromatografía o re-cristalización, o el uso de grandes cantidades de carbón activado.

Así, iniciando a partir de un producto de terbinafina base prima que contiene por ejemplo de cerca de 10 ppm a cerca de 200 ppm, e.g. de cerca de 50 ppm de paladio, y/o de cerca de 10 ppm a cerca de 100 ppm, e.g. de cerca de 30 ppm de cobre, una destilación de camino corto de una etapa conduce a un producto que contiene menos de 1 ppm de cobre, y/o menos de 2 ppm según se determina utilizando métodos analíticos convencionales tales como espectroscopia de absorción atómica.

Los otros contaminantes, si están presentes, en particular compuestos orgánicos tales como (metil) (naftalen-1-ilmetil)amina **(por elproducto 1)**; 2,2,7,7-tetrametilocta-3,5diino **(por elproducto 2);** y el isómero Z de la terbinafina, por lo tanto pueden ser eliminados solo parcialmente o no del todo, e.g. para el producto 1 y el isómero Z de la terbinafina.

La invención por lo tanto incluye i.a.:

- Un proceso para la purificación de terbinafina el cual comprende someter la terbinafina cruda en la forma de base libre a destilación y recuperar el producto resultante en la forma de base libre o de sal por adición de ácido;

- Un proceso de la invención el cual comprende una destilación de camino corto;

- Un proceso como se definió antes en donde la destilación se efectúa a una temperatura de 100°C y a presión reducida;

- Un proceso como se definió antes en donde la terbinafina cruda se prepara utilizando un catalizador que contiene paladio y/o cobre;

- Un proceso como se definió antes en donde el producto purificado contiene menos de 2 ppm de paladio y/o menos de 1 ppm de cobre;

- Un proceso como se definió antes en donde la terbinafina cruda contiene mas de 2 ppm de paladio y/o mas de 1 ppm de cobre, y el producto purificado resultante contiene menos de 2 ppm de paladio y/o menos de 1 ppm de cobre:

- Un proceso como se definió antes en donde se prepara por destilación por lote o corrida 5 Kg de producto purificado en la forma de base libre, preferiblemente por lo menos 50 Kg, especialmente por lo menos 200 Kg,

- Un proceso como se definió antes en donde la terbinafina cruda en la forma de base libre se prepara por reacción de (E)-N-(3-halo-2-propenil)-N-metil-N-(1-naftilmetil)amina con 3,3-dimetil-1-butino en presencia de un catalizador de paladio y/o cobre;

- La terbinafina purificada en la forma de base libre o de sal por adición de ácido siempre que sea preparada por un proceso como el descrito antes; y

- La terbinafina en la forma de base libre o de sal por adición de ácido que comprende menos de 2 ppm de paladio y/o menos de 1 ppm de cobre, siempre que sea obtenida de un producto crudo en la forma de base libre que comprenda mas de 2 ppm de paladio y/o mas de 1 ppm de cobre.

EXPLICACION DE LA FIGURA

1. Flujo del destilado
2. Conexión para la bomba de vacío
3. Entrada de calor
4. Condensador
5. Espacio bajo presión reducida
6. Contacto deslizante enrollado (distribuyen el producto crudo en forma pareja para formar una película)
7. Camisa de calentamiento
8. Sello liquido entrada

9. Reborde para engranaje
10. Entrada producto crudo
11. Salida para el medio de calentamiento
12. Flujo del residuo
13. Entrada para el agua de enfriamiento
14. Salida para el agua de enfriamiento.

Los siguientes ejemplos ilustran la invención. Todas las temperaturas están en grados centígrados 1000 mbar = a 750.06 mmHg; ppm = partes por minuto.

Ejemplo 1: Destilación por lote (escala de laboratorio

Se mezclaron 100 g de terbinafina base cruda que contiene 0.3 área-porcentaje de (metil) (naftalen-1-ilmetil)amina **(por el producto 1)** con 50 g de aceite de maní y la mezcla se calentó a 142° a 0.3 mbar de presión (temperatura de la camisa 190°) después de 2 horas, se purificaron 96.4 g de terbinafina base como un destilado amarillento y se obtuvieron 21.4 g de un residuo café oscuro. Debido al impacto térmico durante la destilación por lotes (2 horas a 142°) el destilado contiene cerca de 1 área-porcentaje de (metil) (naftalen-1-ilmetil)amina **(por el producto 1)** según se determinó por cromatografía de gases (condiciones experimentales: como las del ejemplo 2).

Para producción a gran escala el tiempo de destilación y el impacto térmico serian considerablemente más altos. Se puede esperar como consecuencia una concentración significativamente más alta por el producto 1 a menos que el tiempo de destilación se mantenga corto, tal como con e.g. una destilación de paso corto.

La terbinafina base cruda usada como el material inicial se preparo por reacción de (E)-N-(3-cloro-2-propenil)-N-metil-1-naftalenmetanamina y 3,3-dimetil-1-butino en n-butilamina y agua en presencia de cantidades catalíticas de yoduro de cobre (I) y cloruro de bis-(trifenilfosfina) paladio (II) a lo largo de las líneas como se describe en el ejemplo 13 de EP 421302 A2, pero sin someter el producto resultante a cromatografía en silicagel.

Ejemplo 2: Destilación por camino corto (escala de laboratorio)

En un evaporador de capa delgada comercial (de Leybold-Heraeus GmbH, Hanau, Germany: diámetro del tanque calentado 7 cm; longitud 25 cm; dedo de enfriamiento a 50°; presión 0.2 mbar; rotor Teflón® a 450 rpm) se mezclaron 179 g de terbinafina base cruda (preparada como se describió en el ejemplo 1 anterior con 8.9 g de aceite de maní y la mezcla se calentó a 50°. Después de la evacuación de todo el sistema hasta 0.2 mbar se inicio la destilación por goteo lento a la mezcla en la zona de temperatura alta (temperatura de la camisa 160°) donde la terbinafina base se calentó al punto de ebullición por solo unos cuantos segundos. Después de 2 horas, se obtuvieron 171 g (95%) de terbinafina base como un destilado amarillento, el cual esta contaminado con **1 ppm de paladio** y menos de **1 ppm de cobre**. La pureza química del destilado es 98.6% de terbinafina base (i.e. el isómero E) según se determino por cromatografía de gases (columna HP-1; metil siloxano entrecruzado; longitud 30 m; espesor de la película 2.65 µm; diámetro interno de la columna 0.53 mm; temperatura del detector de ionización de llama (FID) 300°; temperatura del inyector 250°; gradiente de temperatura 50° a 270°; tasa de calentamiento 20°/min). En adición se obtuvieron 10.5 g de residuo de destilación y 0.4 g de un sublimado aceitoso. El sublimado consiste principalmente de 2,2,7,7-tetrametilocta-3,5diino **(por el producto 2)**.

La pureza total de la terbinafina base según se determino por cromatografía de gases es como sigue:

	Antes de la destilación (producto crudo)	**Después de la destilación (producto puro)**
Por el producto 1 (área-porcentaje	0.1	0.1
Por el producto 2 (ares-porcentaje)	0.7	0.2
Isómero –Z (área-porcentaje	0.3	0.3
Isómero –E (peso-porcentaje)	95.6	98.6
Pd (ppm)	177	1
Co (ppm)	19	<1

Ejemplo 3: Destilación de camino corto (escala industrial)

La destilación de la terbinafina base cruda se llevo a cabo en un aparato de destilación a vacío fino (UIC GmbH KD 150) utilizando una destilación de paso corto con dos evaporadores en serie. Por lo tanto el material se alimento constantemente y se distribuyó a la superficie interior de un evaporador orientado verticalmente. Como el liquido fluye hacia abajo, un sistema de contacto de rodillo deslizante dispuesto axialmente distribuye este liquido como una película fina la cual se mezcla constantemente (ver figura). Por lo tanto este método de destilación suave reduce ambos, la temperatura de evaporación máxima y el tiempo de residencia a alta temperatura.

Los valores de temperaturas iniciales son típicamente el conjunto que sigue:

- Limite interno del tanque de alimentación: 70°,
- Limite interno del receptor de producto: 80°; limite de la camisa del tanque de residuo: 80°;
- Limite superior e inferior de los evaporadores 1 y 2: 100°;
- Limite de la camisa de los evaporadores 1 y 2: 160°

Después del control del aparato total para desocupar y limpiar se controla el vacío máximo de ambos evaporadores lo cual se puede alcanzar por bombas de difusión:

- Antes y después del evaporador 1: 1.6×10^{-1} mbar;
- Antes del evaporador 2: 2.6×10^{-2} mbar;
- Después del evaporador 2: 4.7×10^{-3} mbar.

Luego se transfiere una mezcla de 872.5 Kg de terbinafina base cruda (preparada análogamente a como se describió en el Ejemplo 1 anterior) y 120 kg de aceite de maní al tanque de alimentación. El aceite de maní asegura que no se formen incrustaciones dentro de los evaporadores. La trampa de enfriamiento se llena con una mezcla de 20 a 30 Kg de hielo seco y cerca de 30 L de etanol (94%) y se ajustan los valores de temperatura a los siguientes:

- Camisa del receptor de residuos: 40°;
- Camisa del evaporador 1: 120°;
- Condensador del evaporador 1: 50°;
- Camisa del evaporador 2: 155°;
- Condensador del evaporador 2: 45°.

La temperatura interna del receptor principal se fija a 50° ya que el punto de fusión del producto esta alrededor de 42°.

Cuando se alcanzan todas las temperaturas el producto crudo se alimenta al evaporador 1 con un flujo de cerca de 1.5 L/min. El destilado (los demás solventes) del evaporador 1 se pueden colectar en la medida que su volumen sea pequeño. El residuo del evaporador 1 se transfiere al evaporador 2 para destilar la base cruda, la cual se recoge en el receptor principal calentado (1.4 L/min) como un liquido amarillo.

Cuando se destila toda la mezcla cruda (alrededor de 11 horas) el residuo del evaporador 2 se transfiere al tanque de alimentación y se destila de nuevo. Por lo tanto la temperatura de la camisa del evaporador 1 se reduce a 110° y la temperatura de la camisa del evaporador 2 se reduce a 140°.

Después que se completa la destilación del residuo (alrededor de 2 horas) el nuevo residuo se recicla a través de los evaporadores hasta que el flujo del producto ha alcanzado alrededor de 0.2 L/h. antes que se pueda iniciar el reciclaje se reduce la temperatura de la camisa del evaporador 1 a 100° y la temperatura del condensador del evaporador 2 se aumenta a 60°. Durante el reciclaje el destilado recibido llega a ser oscuro.

Al final de la destilación (sobre todo cerca de 22.5 h), el aparato se libera con nitrógeno. El producto del receptor principal se lleva a 50° dentro de tambores. Se toma una muestra y se pesan los tambores. La **pureza** química de la base libre es de 97% o mas alta (aquí fue de 98.4%) según se determino por cromatografía de gases. El producto fue 856.1 Kg. La cantidad de **cobre** y/o **paladio** remanentes fue muy pequeña o indetectable **(menos de 1 ppm)**.

El residuo remanente (alrededor de 120 Kg de *aceite de maní*; aquí fue 128 Kg), el destilado del evaporador 1 y los condensados de las trampas de enfriamiento se combinan e incineran. Después de 5 o 6 lotes se efectúa una limpieza del aparato.

Ejemplo comparativo: Tratamiento con carbón activado (escala de laboratorio)

Se agregaron 10 g de carbón activado (Norit Supra®) a 404 g de una solución de terbinafina base cruda en ciclohexano (preparada análogamente a como se describió en el Ejemplo 1 anterior a partir de 100 g de (E)-N-(3-cloro-2-propenil)-N-metil-1-naftaleno-metanamina). La mezcla se agito por 17 horas a 20 – 25° y luego se filtró. Después de evaporar el solvente a presión reducida se obtuvieron 110.5 g (89%) de terbinafina base, la cual está contaminada con **14 ppm de paladio**. La **pureza** química del residuo oleoso es del 95% según se determinó por cromatografía de gases (condiciones experimentales: como las del Ejemplo 2).

REIVINDICACIONES

1. Un proceso para la purificación de terbinafina el cual comprende someter la terbinafina cruda en la forma de base libre a destilación y recuperar el producto resultante en la forma de base libre o sal por adición de ácido.

2. Un proceso de acuerdo con la reivindicación 1 el cual comprende una destilación de camino corto.

3. Un proceso de acuerdo con la reivindicación 1 o 2 en donde la destilación se efectúa a una temperatura por encima de 100°C y bajo presión reducida.

4. Un proceso de acuerdo con la reivindicación 1 o 2 en donde la terbinafina cruda se prepara utilizando un catalizador que contiene paladio y/o cobre.

5. Un proceso de acuerdo con la reivindicación 4 en donde el producto purificado contiene menos de 2 ppm de paladio y/o menos de 1 ppm de cobre.

6. Un proceso de acuerdo con la reivindicación 4 en donde la terbinafina cruda contiene mas de 2 ppm de paladio y/o mas de 1 ppm de cobre, y el producto purificado resultante contiene menos de 2 ppm de paladio y/o menos de 1 ppm de cobre.

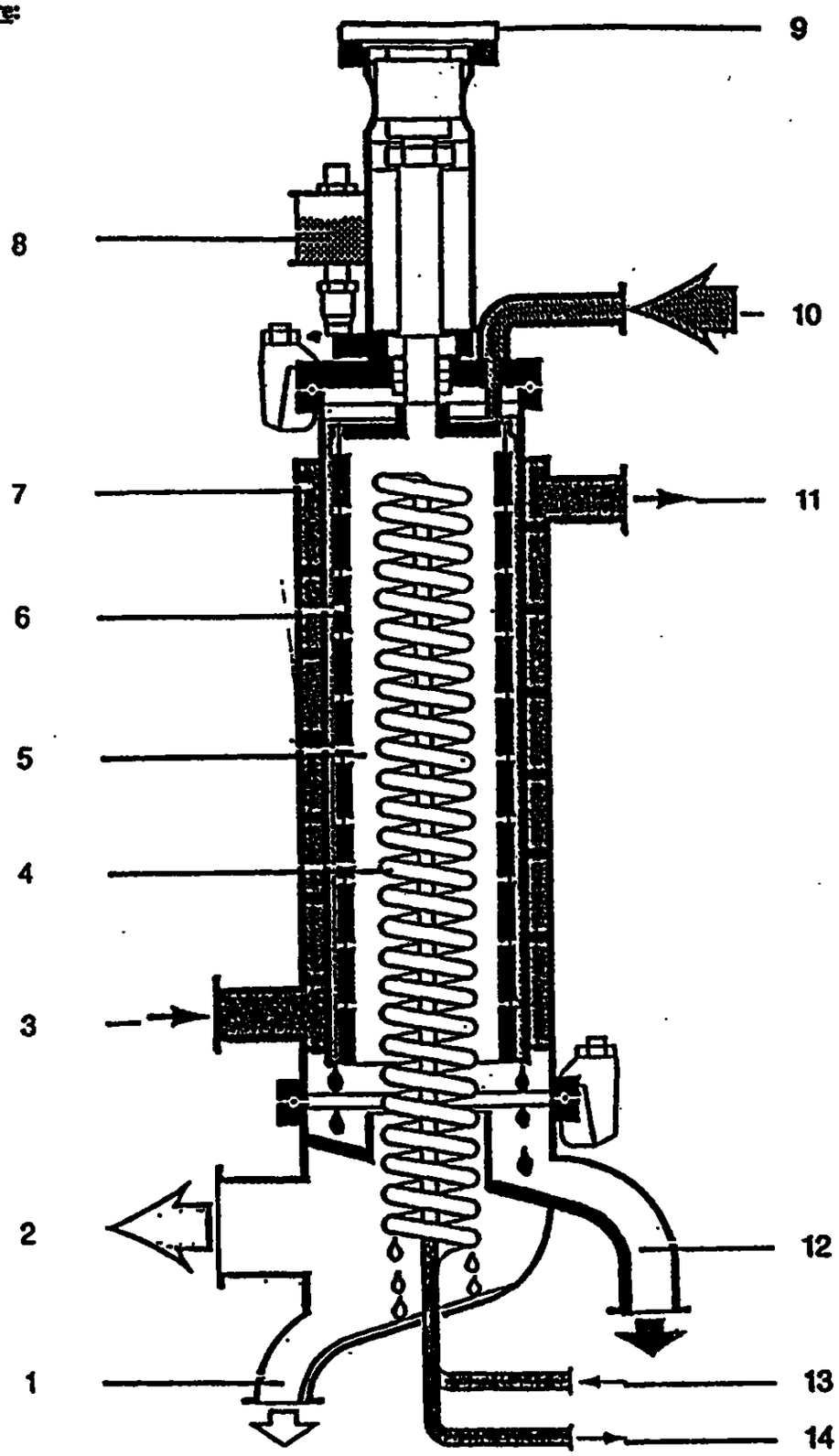
7. Un proceso de acuerdo con la reivindicación 1 o 2 en donde por lo menos se preparan por destilación en lote o corrida 5 kg del producto purificado en la forma de base libre, preferiblemente al menos 50 kg, especialmente al menos 200 Kg.

8. Un proceso de acuerdo con la reivindicación 1 o 2 en donde la terbinafina cruda en la forma de base libre se prepara por reacción de (E)-N-(3-halo-2-propenil)-N-metil-N-(1-naftilmetil)amina con 3,3-dimetil-1-butino en presencia de un catalizador de paladio y/o cobre.

9. La terbinafina purificada en la forma de base libre o sal por adición de ácido siempre que sea preparada por un proceso de acuerdo con cualquiera de las reivindicaciones 1 a 8.

10. La terbinafina en la forma de base libre o sal por adición de ácido que comprende *menos de 2 ppm* de paladio y/o menos de 1 ppm de cobre, siempre que sea obtenida a partir de un producto crudo en la forma de base libre que comprenda mas de 2 ppm de paladio y/o mas de 1 ppm de cobre.

Figure:



PCT

REQUEST

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

For receiving Office use only

International Application No. PCT/EP 2004 / 0 0 9 5 3 7

International Filing Date (27.08.2004) 27 AUG 2004

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)* PD/4 -33305A

Box No. I TITLE OF INVENTION

Purification Process

Box No. II APPLICANT ☐ This person is also inventor

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

Novartis AG
Lichtstrasse 35
4056 Basel
CH

Telephone No. +41 61 324 11 11

Facsimile No. +41 61 322 75 32

Teleprinter No.

Applicant's registration No. with the Office

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

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

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box

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

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

Novartis 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

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

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

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box

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

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

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

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

GRUBB, Philip
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

☐ **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.

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

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

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.)*

BEUTLER, Ulrich
Im Lohgraben 42
4104 Oberwil
CH

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

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

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.)*

PENN, Gerhard
Im Lohgraben 28
4104 Oberwil
CH

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

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

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

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

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

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

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

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

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

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

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

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

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

See Notes to the request form

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:

*(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;*

*(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. VI, there are **more than three 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 the applicant intends to make an indication of the wish that the international application be treated, in certain designated States, as an application for a patent of addition, certificate of addition, inventor's certificate of addition or utility certificate of addition: in such a case, write the name or two-letter code of each designated State concerned and the indication **"patent of addition," "certificate of addition," "inventor's certificate of addition"** or **"utility certificate of addition,"** the number of the parent application or parent patent or other parent grant and the date of grant of the parent patent or other patent grant or the date of filing of the parent application (Rules 4.11(a)(iii) and 49bis.1(a) or (b)).*

*3. If the applicant intends to make an indication of the wish that the international application be treated, in the United States of America, as a continuation or continuation-in-part of an earlier application: in such a case, write "United States of America" or "US" and the indication **"continuation"** or **"continuation-in-part"** and the number and the filing date of the parent application (Rules 4.11(a)(iv) and 49bis.1(d)).*

Continuation of Box No. II
Novartis AG is applicant for all designated States with the exception of: AT (Austria) and US (USA)

Continuation of Box No. III
Novartis Pharma GmbH is applicant for AT (Austria) only.

Box No. V DESIGNATIONS

The filing of this request **constitutes under Rule 4.9(a), the designation** of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

☐ DE Germany **is not designated** for any kind of national protection

☐ KR Republic of Korea **is not designated** for any kind of national protection

☐ RU Russian Federation **is not designated** for any kind of national protection

(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

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 August 2003 (29.08.03)	0320312.2	GB		
item (2)				
item (3)				

☐ 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) ☐ other, see Supplemental Box

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

. . . . . .

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

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

ISA / EP . . . . . .

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

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

Box No. VIII DECLARATIONS

The following **declarations** are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*:		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor :	
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent :	
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application :	
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America) :	
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty :	

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

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

request (including declaration sheets)	:	5
description (excluding sequence listing and/or tables related thereto)	:	10
claims	:	2
abstract	:	1
drawings	:	1
Sub-total number of sheets	:	19
sequence listing	:	
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	:	19

(b) ☐ **only in computer readable form** (Section 801(a)(i))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

(c) ☐ **also in computer readable form** (Section 801(a)(ii))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listing: .....
- ☐ 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):*

		Number of items
1. ☒ fee calculation sheet	:	1
2. ☐ original separate power of attorney	:	
3. ☐ original general power of attorney	:	
4. ☒ copy of general power of attorney; reference number, if any: AV.36671.+46171	:	2
5. ☐ statement explaining lack of signature	:	
6. ☐ priority document(s) identified in Box No. VI as item(s): (1) (will follow)	:	
7. ☐ translation of international application into *(language)*:	:	
8. ☐ separate indications concerning deposited microorganism or other biological material	:	
9. ☐ sequence listing in computer readable form *(indicate type and number of carriers)*		
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* 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 13*ter*	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column	:	
10. ☐ tables in computer readable form related to sequence listing *(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

30.07.2004

GRUBB, Philip AV 36671 + 46171

For receiving Office use only

1. Date of actual receipt of the purported international application: 27 AUG 2004 (27.08.2004)
2. Drawings: ☒ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 March 2005 (10.03.2005)

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WO 2005/021483 A2

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0320312.2 29 August 2003 (29.08.2003) 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 [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): BEUTLER, Ulrich [CH/CH]; Im Lohgraben 42, CH-4104 Oberwil (CH). PENN, Gerhard [AT/CH]; Im Lohgraben 28, CH-4104 Oberwil (CH).

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

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

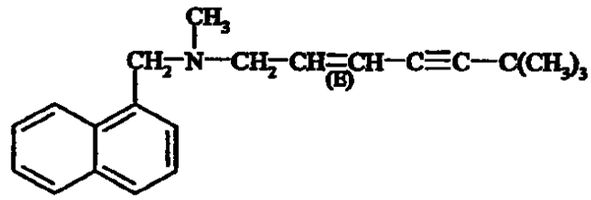
(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

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.

WO 2005/021483 A2

(54) Title: PURIFICATION PROCESS



(I)

(57) Abstract: Purification process for the preparation of the allylamine pharmaceutical terbinafine of formula (I), in free base form or acid addition salt form, by distilling crude terbinafine base, preferably by short path distillation, e.g. at a temperature above 100°C and reduced pressure, e.g. 0.2 mbar, and recovering the purified product in free base or acid addition salt form.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PD/4- 33305A	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/EP2004/009587	International filing date *(day/month/year)* 27.08.2004	Priority date *(day/month/year)* 29.08.2003
International Patent Classification (IPC) or national classification and IPC C07C209/84, C07C211/27		
Applicant NOVARTIS AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

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

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

Date of submission of the demand	Date of completion of this report
18.04.2005	11.08.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Kleidernigg, O Telephone No. +49 89 2399-2143

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/EP2004/009587

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-10 as originally filed

   Claims, Numbers

   1-10 received on 18.04.2005 with letter of 14.04.2005

   Drawings, Sheets

   1/1 as originally filed

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

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

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

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/009587

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

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

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

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/EP2004/009587

Re Item I

As introduction to this report it has to be remarked that the amendment/s concerning claim 1 "up to a temperature where still only limited thermal decomposition is observed" extends beyond the content of the application as originally filed. This amendment infringes Articles 19(2) and 34(2)b) PCT.
In accordance with Rule 70.2c) the international preliminary examination report is drawn up as if the amendment which extends beyond the content of the application as originally filed has not been made.

However, the temperature range from 110°C-170°C as disclosed on page 4, line 7 of the present application can be incorporated in claim 1 in order to satisfy Articles 19(2) and 34(2)b) PCT.

Re Item V

D1: EP-A-1 236 709 = (16)
D2: Tetrahedron Letters, Vol. 37(1), pp 57-58, 1996 = (15a)

The present application is directed to a process for the purification of terbinafine which comprises subjecting crude terbinafine in free base form to distillation at elevated temperature and under correspondingly reduced pressure and recovering the resultant product in free base or acid addition salt form.

(16) (i.e. cl. 1-6; Ex. 1-c)
D1 (cf. passages indicated in the ISR) represents the closest prior art and differs form the matter of claim 1 insofar that no distillation purification step is disclosed.
Thus, the matter of claims 1-8 fulfills the criteria of Article 33(2) PCT.

Claim 9 is directed to the use of a process according to claim 1, which comprises short path distillation in the preparation of purified terbinafine in free base or acid addition salt form is novel with respect to the closest prior art of D1 due to the reasons as outlined above for claims 1-8.
Thus, the matter of claim 9 is novel as well as claim 10 which is a dependent claim of claim 9.

The problem to be solved by the present invention may therefore be regarded as the provision of an improved process for the purification of terbinafine.

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT), because as outlined in the description of the present application, the special structure of terbinafine comprises a double and a triple bond, and compounds showing that arrangement tend to decompose under certain distillation conditions, e.g. high temperature and ambient pressure. The applicant did not show unambiguously that the claim over its whole scope is a solution to the above stated technical problem. The use of a short path distillation in the preparation of purified terbinafine (claim 9) does also not limit the process to a certain temperature and is also not inventive.
However, the limitation to the temperature range of 100-170°C as outlined on page 4, line 7 of the present application, would satisfy the requirements of Article 33(3) PCT.

Re Item VIII

Claim 9 includes all the features of claim 1. Hence, category should be changed in claim 9 and it should be reformulated as a claim dependent on claim 1 (Article 6 PCT).

Claims:

1. A process for the purification of terbinafine which comprises subjecting crude terbinafine in free base form to distillation at elevated temperature and under correspondingly reduced pressure, up to a temperature where still only limited thermal decomposition is observed, and recovering the resultant product in free base or acid addition salt form.

2. A process according to claim 1 which comprises short path distillation.

3. A process according to claim 1 or 2 wherein distillation is effected at a temperature above 100°C and under reduced pressure.

4. A process according to claim 1 or 2 wherein the crude terbinafine is prepared using a palladium- and/or a copper-containing catalyst.

5. A process according to claim 4 wherein the purified product contains less than 2 ppm palladium and/or less than 1 ppm copper.

6. A process according to claim 4 wherein the crude terbinafine contains more than 2 ppm palladium and/or more than 1 ppm copper, and the resultant purified product contains less than 2 ppm palladium and/or less than 1 ppm copper.

7. A process according to claim 1 or 2 wherein at least 5 kg purified product in free base form is prepared per distillation batch or run, preferably at least 50 kg, especially at least 200 kg.

8. A process according to claim 1 or 2 wherein the crude terbinafine in free base form is prepared by reaction of (E)-N-(3-halo-2-propenyl)-N-methyl-N-(1-naphthylmethyl)amine with 3,3-dimethyl-1-butyne in the presence of a palladium and/or a copper catalyst.

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9. Use of a process according to claim 1 which comprises short path distillation in the preparation of purified terbinafine in free base or acid addition salt form.

10. Use of a process according to claim 9 in the preparation of purified terbinafine in free base or acid addition salt form comprising less than 2 ppm palladium and/or less than 1 ppm copper.

(+C. with handwritten remarks.)

17.04.2006
PD/4 -33305A
Lucien Vallet

OFFACT
PCT
EP2004/009587 TY

17. Feb. 2005

F/F	M/D	F/L	PS	Copy

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
NOVARTIS AG
Corporate Intellectual Property
Attn. Grubb, Philip
CH-4002 Basel
SWITZERLAND

Date of mailing *(day/month/year)*	17/02/2005
Applicant's or agent's file reference: PD/4-33305A	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No.: PCT/EP2004/009587	International filing date *(day/month/year)* 27/08/2004
Applicant: NOVARTIS AG	

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

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

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

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

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

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

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

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

4. **Reminders**

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

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority	Authorized officer
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	Angela Lopez Navarro

Form PCT/ISA/220 (January 2004) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

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

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

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

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

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

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

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

When?

17.2.05 — 2 mo — 17.4.05

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

under Art. 19

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

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

How?

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

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

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

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

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

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

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

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

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

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

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

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

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

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

It must be in the language in which the International appplication is to be published.

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

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

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

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

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

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

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

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

PCT Art 18

PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	17.2.05
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/009587	27.08.2004	29.08.2003

International Patent Classification (IPC) or both national classification and IPC
C07C209/84, C07C211/27

Applicant
NOVARTIS AG

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

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

2. **FURTHER ACTION**

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

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later. i.e. by 29.6.05 (17.5.05; 29.8.03; i.e. 29.6.05)

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

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

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Kleidernigg, O Telephone No. +49 89 2399-2143

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

(+ 2 Notif. of Transmittal It's)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/EP2004/009587

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

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

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	9,10
Inventive step (IS)	Yes:	Claims	2-8
	No:	Claims	1,9,10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/009587

Re Item V

D1: EP-A-1 236 709 = (16)
D2: Tetrahedron Letters, Vol. 37(1), pp 57-58, 1996 = (15a)

The present application is directed to a process for the purification of terbinafine which comprises subjecting crude terbinafine in free base form to distillation and recovering the resultant product in free base or acid addition salt form.

D1 (16) (cf. passages indicated (cl. 1-6 + Ex. 1-6) in the ISR) represents the closest prior art and differs form the matter of claim 1 insofar that no distillation purification step is disclosed.
Thus, the matter of claims 1-8 fulfills the criteria of Article 33(2) PCT.

Claim 9 is directed to a product-by-process claim concerning terbinafine. However, terbinafine is a known compound (D1, D2; cf. passages indicated in the ISR) and per se not novel. A product-by-process claim is only allowable, if the product per se is fulfilling the requirements of novelty and inventive step.
Thus, the matter of claim 9 is not novel. ?

Claim 10 is directed to terbinafine free base showing a specific degree of chemical purity. However, it is the common general knowledge that any chemical compound obtained by a chemical reaction would normally contain impurities for various reasons. It is not possible for thermodynamical reasons to obtain a compound which is completely pure. The IPEA is therefore of the opinion that a document (D1, D2) disclosing a chemical compound and its manufacture made this compound available to the public within the meaning of Article 33(2) PCT in all grades of purity as desired by a person skilled in the art.
Thus, the matter of claim 10 is not novel. ?

The problem to be solved by the present invention may therefore be regarded as the provision of an improved process for the purification of terbinafine.

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT), because as outlined in the description of the present application, the special structure of terbinafine comprises a double and a triple

bond, and compounds showing that arrangement tend to decompose under certain distillation conditions, e.g. high temperature and ambient pressure. The applicant did not show unambiguously that the claim over its whole scope is a solution to the above stated technical problem.

?!

so for specific temperature and pressure range ?

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
PD/4-33305A		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2004/009587	27/08/2004	29/08/2003
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 3 sheets.

[X] 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, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box II).

3. [ ] **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,
   [ ] the text is approved as submitted by the applicant.
   [X] the text has been established by this Authority to read as follows:

   PROCESS FOR THE PURIFICATION OF TERBINAFINE

5. With regard to the **abstract**,
   [X] 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 No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the drawings to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [X] none of the figures is to be published with the abstract.

PCT
All / Searches

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/009587 A6

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C209/84 C07C211/27

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A X	EP 1 236 709 A (DINAMITE DIPHARMA S.P.A.) p. 2.3.01 = (16) = D1 4 September 2002 (2002-09-04) claims 1-6; examples 1-6	1-8 9,10
A	ALAMI M ET AL: "A Two-Step Synthesis of Terbinafine" → (15a) D2 TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 37, no. 1, January 1996 (1996-01), pages 57-58, XP004030473 ISSN: 0040-4039	1-8
X	page 58, compound 1a	9,10

☐ 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 February 2005	17/02/2005

Name and mailing address of the ISA	Authorized officer
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	Kleidernigg, O

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REP RT

Information on patent family members

International Application No
PCT/EP2004/009587

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1236709 A	04-09-2002	IT MI20010430 A1	02-09-2002
		CA 2373813 A1	02-09-2002
		EP 1236709 A2	04-09-2002
		JP 2002308835 A	23-10-2002
		US 2002123651 A1	05-09-2002

SUPERINDUSTRIA Y COMERCIO
Radicacion : 06019444 0000000
Fecha (AMD): 2006-02-27 16:01:00 Folios: 50
Tramite : 401 PCT-PATENT 3/9 FASE NAC 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN (✓) 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 se presenta la solicitud.	( )	( )
-Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
ESQUEMA DE TRAZADO ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica del Esquema Trazado.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )

Firma Responsable: _____

Fecha: _____

Industria y Comercio
SUPERINTENDENCIA

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INFORME DE PROTOCOLO

Expediente 06 – 019204

Fecha: 27 de Febrero de 2.006

Se certifica que:

Desde fecha 16 de abril de 1997,

del folio 90.643 al folio 90.650 del libro de Protocolo Nº 311, obra el poder Nº 17.398 conferido por NOVARTIS AG (NOVARTISSA) (NOVARTIS INC.) domiciliado(a) en Basilea - Suiza al doctor JIMENA ESCOBAR URIBE y/o IGNACIO ESCOBAR URIBE.

Representante en Santafé de Bogotá D.C. Los mismos.

Facultad para desistir y sustituir SI.

Revisado ramosjuanp.

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia

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REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y C MERCI

Bogotá,
2020

Doctor(a)
ESCOBAR URIBE JIMENA
Apoderado(a) y/o Representante de
NOVARTIS AG

REFERENCIA	Radicación No.	6 19204
	Solicitud internacional	EP2004/009587
	Fecha inicio fase nacional	29/03/2006
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	4322

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

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

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

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

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

El anterior requerimiento fue notificado por fijación en lista de fecha 21 ABR. 2006
jramos