Industria y Comercio

SUPERINTENDENCIA

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21 EXPEDIENTE Nº 04-11525

54 TÍTULO COMBINACIONES QUE COMPRENDEN EPOTILONAS Y SUS USOS FARMACEUTICOS

51 CLASIFICACIÓN INTERNACIONAL A61P 35/00

71 SOLICITANTE NOVARTIS AG

DOMICILIO BASILEA, SUIZA

74 APODERADO JIMENA ESCOBAR URIBE

22 BOGOTÁ, D C FEBRERO ,2004

(FORMA P 10)

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

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

[ ] Capítulo I [X] Capítulo II

2 SOLICITANTE (71)	Nombre: NOVARTIS AG Dirección: Lichtstrasse 35 CH-4056 Nacionalidad o Domicilio: Basilea, Suiza. Lugar de Constitución: Suiza Teléfono: 41613241111 Fax: 4116 13227532 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:	

5 PCT (86)

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6 TÍTULO (54): COMBINACIONES QUE COMPRENDEN EPOTILONAS Y SUS USOS FARMACÉUTICOS

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8 Prioridad SI [X] NO [ ]	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
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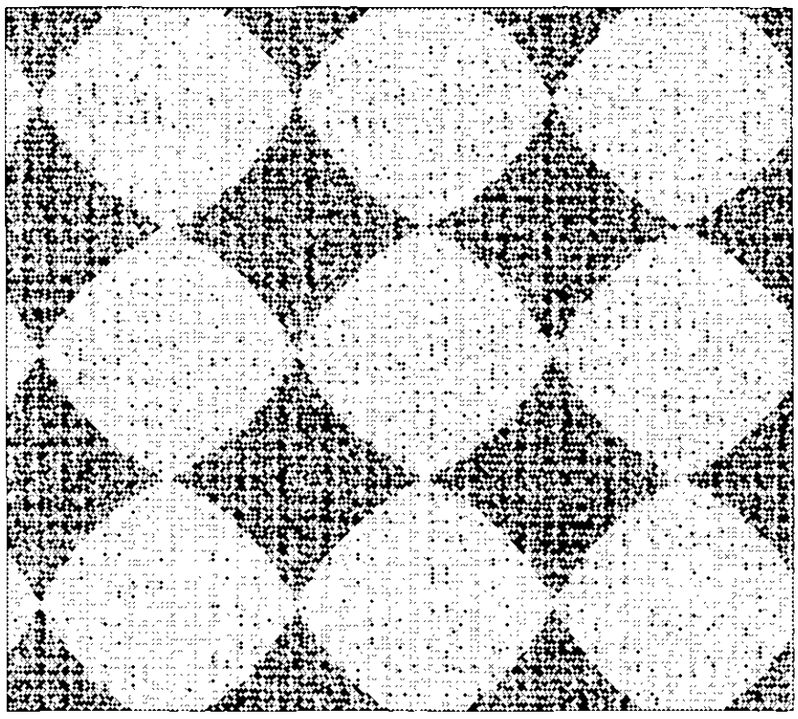
	ESTADOS UNIDOS DE AMÉRICA	Julio 19, 2001	60/306,560

9 Comprobante de pago No. 04 - 2865 Fecha Enero 16, 2004

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 Prot. 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).
- [x] 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 * Copia y traducción de la opinión escrita.

11 FIGURA CARACTERÍSTICA



12 Solicito la concesión de la patente

NOMBRE JIMENA ESCOBAR URIBE

FIRMA

C.C. 38.[illegible] de Ubaté T.P. 69.328

As. 2521/PCT

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 04011525 00000000 Folios: 92
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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FECHA : ENERO 15 DE 2004

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ESCOBAR URIBE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	4991327	14/01/2004	6,094,000.

C O N C E P T O

CANT.	REMTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
		TOTAL : $	422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ANEXOS

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5.) **WOOD, Jeanette, Marjorie**
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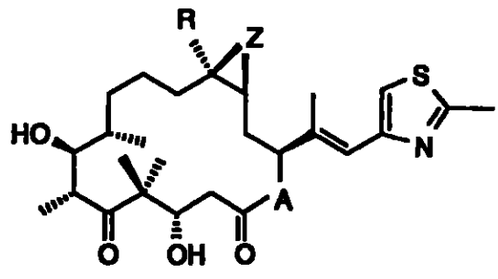
Solicito expresamente a nombre de la sociedad **NOVARTIS AG.**, sociedades constituidas de conformidad con las leyes de Suiza, domiciliada en Lichtstrasse 35, CH-4056 Basilea, Suiza, el otorgamiento de Patente para la invención titulada **"COMBINACIONES QUE COMPRENDEN EPOTILONAS Y SUS USOS FARMACÉUTICOS".**

Clase: A61P 35/00

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

RESUMEN

La invención se refiere a una combinación que comprende (a) un bisfosfonato, un compuesto de platino o un compuesto vasculoestático, y (b) un derivado de epotilona de la fórmula I,



(I)

en donde A representa O u NR_N, en donde R_N es hidrógeno o alquilo inferior, R es hidrógeno o alquilo inferior, y Z es O, o un enlace, en donde los ingredientes activos (a) y (b) están presentes en cada caso en forma libre o en la forma de una sal farmacéuticamente aceptable y opcionalmente por lo menos un vehículo farmacéuticamente aceptable para el uso simultáneo, separado o secuencial, en particular para el retraso de la progresión o para el tratamiento de una enfermedad proliferativa, especialmente una enfermedad de tumor sólido; una composición farmacéutica, un paquete comercial o un producto que comprende dicha combinación; el uso de dicha combinación para la preparación de un medicamento para el retraso de la progresión o para el tratamiento de una enfermedad proliferativa y a un método para el tratamiento de un animal de sangre caliente.

COMBINACIONES QUE COMPRENDEN EPOTILONAS Y SUS USOS FARMACEUTICOS

DESCRIPCION

La invención se refiere a una combinación que comprende (a) un bisfosfonato, un compuesto de platino o un compuesto vasculoestático y (b) un derivado de epotilona de la fórmula I y opcionalmente por lo menos un vehículo farmacéuticamente aceptable para uso simultáneo, separado o secuencial, en particular para el retraso de la progresión o tratamiento de una enfermedad proliferativa, especialmente una enfermedad de tumor sólido; una composición farmacéutica que comprende dicha combinación; el uso de dicha combinación para la preparación de un medicamento para el retraso de la progresión o tratamiento de una enfermedad proliferativa; un paquete comercial o producto comprendiendo dicha combinación como una preparación combinada para uso simultáneo, separado o secuencial; y a un método para el tratamiento de un animal de sangre caliente, especialmente un ser humano.

A pesar del amplio uso de Taxol® y Taxotere®, en el tratamiento de muchos diferentes tipos de tumores, el impacto de taxanos en la supervivencia de pacientes ha sido modesto, y una gran mayoría de tumores metastáticos permanecen incurables. El tratamiento con taxano está asociado con un número de efectos laterales importantes, tales como neuropatía periférica y estomatitis,

y la efectividad de los taxanos puede ser severamente limitada por mecanismos de resistencia de fármaco que se desarrollan rápidamente, involucrando posiblemente mutaciones de tubulina o la sobre-expresión de fosfoglicoproteínas que funcionan como bombas de flujo de fármaco. En vista de estas limitaciones así como en vista de los efectos laterales comúnmente observados con terapias de combinación estándares, existe claramente la necesidad de la identificación de combinaciones novedosas que exhiban un perfil total mejorado, incluyendo un espectro más amplio de la actividad antitumoral, eficacia contra tumores resistentes a múltiples fármacos y una seguridad y tolerabilidad más altas.

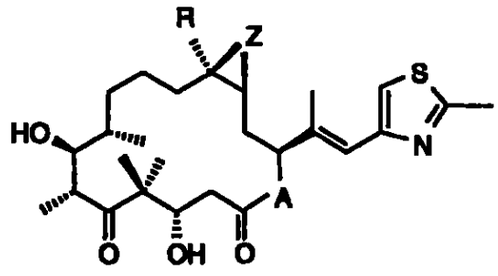
La eficacia terapéutica de bisfosfonatos ha sido demostrada en el tratamiento de la enfermedad de Paget del hueso, hipercalcemia inducida por tumor, metástasis de hueso, y mieloma múltiple (H. Fleisch in Bisphosphonates in Bone Disease. From the Laboratory to the Patient. Eds: The Parthenon Publishing Group, New York/London, 1997, pág. 68 a 163).

La directa evidencia de papel del Factor de Crecimiento Endotelial Vascular (VEGF) como un factor de angiogénesis de tumor in vivo ha sido obtenida a partir de estudios en donde se inhibió la expresión de VEGF o la actividad de VEGF. Esto se logró con anticuerpos con actividad de VEGF, con mutantes de VEGFR-2 dominantes-negativos que inhiben la transducción de señal, o con el uso de técnicas de ARN de antisentido-VEGF. Las pequeñas moléculas que inhiben la cinasa de tirosina de VEGF se describen

en, por ejemplo, WO 98/35958. Una de estas moléculas es conocida como PTK787.

El efecto de estabilización de microtúbulo de las epotilonas primero fue descrito por Bollag y otros, Cancer Research 55, 1995, 2325-33. Un programa de tratamiento adecuado de diferentes tipos de tumores, especialmente tumores que son refractarios al tratamiento a través de otros quimioterapéuticos, en particular TAXOL™, se describe en WO 99/43320.

La presente invención se refiere a una combinación, tal como una preparación combinada o una composición farmacéutica, que comprende (a) un bisfosfonato, un compuesto de platino o un compuesto vasculoestático, y (b) un derivado de epotilona de la fórmula I:



(I)

en donde A representa O u NR_N, en donde R_N es hidrógeno o alquilo inferior, R es hidrógeno o alquilo inferior, y Z es O, o un enlace, en donde los ingredientes activos (a) y (b) están presentes en cada caso en forma libre o en la forma de una sal farmacéuticamente aceptable y opcionalmente por lo menos un vehículo farmacéuticamente aceptable; para uso simultáneo, separado o

secuencial.

A menos que se indique otra cosa, en la presente descripción los radicales orgánicos y compuestos designados como "inferiores" contienen no más de 7, de preferencia no más de 4 átomos de carbono.

Un compuesto de la fórmula I en donde A representa O, R es hidrógeno y Z es O, es conocido como epotilona A; un compuesto de la fórmula I en donde A representa O, R es metilo y Z es O es conocido como epotilona B; un compuesto de la fórmula I, en donde A representa O, R es hidrógeno y Z es un enlace es conocido como epotilona C; un compuesto de la fórmula I, en donde A representa O, R es metilo y Z es un enlace es conocido como epotilona D.

El término "una preparación combinada", como se utiliza aquí, define especialmente un "equipo de partes" en el sentido de que los patrones de combinación (a) y (b) como se definieron anteriormente pueden ser dosificados independientemente o a través del uso de diferentes combinaciones fijas con cantidades distinguidas de los patrones de combinación (a) y (b), es decir, simultáneamente o en puntos diferentes de tiempo. Las partes del equipo de partes entonces pueden ser, por ejemplo, administradas simultánea o cronológicamente, es decir en puntos de tiempo diferentes y con intervalos de tiempo iguales o diferentes para cualquiera del equipo de partes. Muy preferiblemente, los intervalos se seleccionan de manera que el efecto sobre la enfermedad tratada en el uso combinado de las partes sea mayor que el efecto que podría ser

obtenido a través del uso de sólo alguno de los patrones de combinaciones (a) y (b). La relación de las cantidades totales del patrón de combinación (a) al patrón de combinación (b) que será administrada en la preparación combinada puede ser variada, por ejemplo, con el fin de cubrir las necesidades de una sub-población de pacientes que será tratada o la necesidad del paciente individual que sus diferentes necesidades pueden ser la edad, sexo, peso del cuerpo, etc., de los pacientes. De preferencia, existe por lo menos un efecto benéfico, por ejemplo, una mejora mutua del efecto de los patrones de combinación (a) y (b), en particular un sinergismo, por ejemplo, un efecto más que aditivo, efectos ventajosos adicionales, menos efectos laterales, un efecto terapéutico combinado en una dosis no efectiva de uno o ambos de los patrones de combinación (a) y (b) y muy preferiblemente un fuerte sinergismo de los patrones de combinación (a) y (b).

El término "enfermedad de tumor sólido" especialmente significa cáncer de pecho, cáncer de ovario, cáncer de colon y generalmente el tracto gastrointestinal, incluyendo cáncer gástrico, cáncer de servis, cáncer de pulmón, por ejemplo cáncer de pulmón de célula pequeña y cáncer de pulmón de célula no pequeña, cáncer de páncreas, cáncer renal, glioma, melanoma, cáncer de cabeza y cuello, cáncer de vejiga, cáncer hepatocelular, cáncer de próstata y sarcoma de Kaposi. Preferiblemente, la enfermedad proliferativa que será tratada con una combinación comprendiendo un compuesto de platino es cáncer ovárico, cáncer de pulmón, cáncer de cabeza o

cuello, cáncer de servís, cáncer de próstata, cáncer de colon, cáncer de pecho, cáncer renal, tumores carcinoides, cáncer gástrico o cáncer hepatocelular. Preferiblemente, la enfermedad proliferativa que será tratada con una combinación comprendiendo un bisfosfonato es cáncer de pecho, cáncer ovárico o cáncer de pulmón. En otra modalidad preferida de la invención, la enfermedad proliferativa que será tratada con una combinación de la invención comprendiendo un compuesto vasculoestático, en particular PTK787, es cáncer ovárico, cáncer de pecho, cáncer de pulmón, cáncer de cabeza o cuello, cáncer de ceviz, cáncer de próstata o cáncer de colon.

El término "enfermedad proliferativa" como se utiliza aquí, comprende las enfermedades de tumor sólido listadas anteriormente y además la enfermedad de Paget de huesos, hipercalcemia inducida por tumores, metástasis de huesos, y mieloma múltiple.

El término "una enfermedad asociada con angiogénesis desregulada" se refiere en especial a enfermedades causadas por neurovascularisación ocular, especialmente retinopatías, tales como retinopatía diabética o degeneración macular relacionada con la edad, psoriaris, hemangioblastoma, tal como hemangioma, trastornos proliferativos de célula mesangial, tales como enfermedades renales crónicas o agudas, por ejemplo, nefropatía diabética, nefroesclerosis maligna, síndromes de microangiopatía trombótica o rechazo a trasplantes, o en especial a enfermedad renal inflamatoria, tal como glomerulonefritis, especialmente glomerulonefritis

mensagioproliferativa, síndrome hemolítico-urémico, nefropatía diabética, nefroesclerosos hipertensa, ateroma, restenosis arterial, enfermedad autoinmune, inflamación aguda, trastornos fibróticos (por ejemplo, cirrosis hepática), trastornos neurodegenerativos, y especialmente enfermedades proliferativas, en especial aquellas enfermedades proliferativas que comprenden tumores que expresan c-kit, KDR o flt-1.

El término "bisfosfonato" como se utiliza aquí, incluye, pero no se limita a ácido etridónico, ácido clodrónico, ácido tiludrónico, ácido pamidrónico, ácido alendrónico, ácido ibandrónico, ácido risedrónico y ácido zoledrónico. El "ácido etridónico" puede ser administrado, por ejemplo, en la forma como se vende, por ejemplo bajo el nombre comercial de DIDRONEL™. El "ácido clodrónico" puede ser administrado, por ejemplo en la forma como se vende, por ejemplo bajo el nombre comercial de BONEFOS™. El "ácido tiludrónico" puede ser administrado, por ejemplo, en la forma como se vende, por ejemplo bajo el nombre comercial de SKELID™. El "ácido pamidrónico" puede ser administrado, por ejemplo, en la forma como se vende, por ejemplo bajo el nombre comercial de AREDIA™. El "ácido alendrónico" puede ser administrado, por ejemplo, en la forma como se vende, por ejemplo bajo el nombre comercial de FOSAMAX™. El "ácido ibandrónico" puede ser administrado, por ejemplo, en la forma como se vende, bajo el nombre comercial de BONDRANAT™. El "ácido risedrónico" puede ser administrado, por ejemplo, en la forma como se vende, por ejemplo bajo el nombre

comercial de ACTONEL™. El "ácido zoledrónico" puede ser administrado, por ejemplo, en la forma como se vende, por ejemplo bajo el nombre comercial de ZOMETA™.

El término "compuesto de patino" como se utiliza aquí, representa carboplatino, cisplatino o oxaliplatino.

El término "carboplatino" como se utiliza aquí, se refiere al agente antineoplástico cis-diamina (1,1-ciclobutan-dicarboxilato)platino (II), el cual se describe en, por ejemplo, patente de E.U.A. 4,140,707 o por R. C. Harrison y otros, in Inorg. Chim. Acta 46, L15 (1980). Este fármaco puede ser administrado, por ejemplo, en la forma como se vende bajo el nombre comercial de CARBOPLAT™ o PARAPLATIN™.

El término "oxaliplatino" como se utiliza aquí, se refiere al agente antineoplástico también conocido como oxalatoplatino, el cual se describe en, por ejemplo, patente de E.U.A. 5,716,988. Este fármaco puede ser administrado por ejemplo en la forma como se describe en la patente de E.U.A. citada o en la forma como se vende, bajo el nombre comercial de ELOXANTINE™ o 1-OHP™.

El término "cisplatino" como se utiliza aquí, se refiere al agente antineoplástico también conocido como cis-diamindicloroplatino, dicho compuesto y su uso como agente antineoplástico se describe por ejemplo en DE 2,318,020.

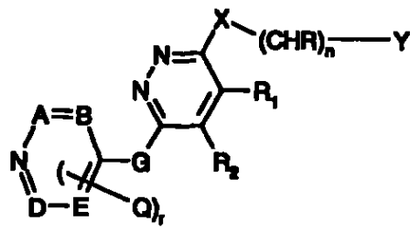
El término "compuestos vasculoestáticos" como se utiliza aquí, comprende, pero no se limita a, ingredientes activos que reducen la actividad del VEGF, inhibidores de metaloproteinasa y otros

compuestos que tengan un efecto vasculoestático.

El ingrediente activo, que reduce la actividad del VEGF, especialmente se selecciona del grupo que consiste de compuestos que inhiben la cinasa de tirosina del receptor de VEGF, compuestos que inhiben un receptor de VEGF y compuestos que se unen a VEGF. El ingrediente activo, que reduce la actividad del VEGF es en particular uno de aquellos compuestos, proteínas y anticuerpos monoclonales que genérica y específicamente se describen en WO 98/35958 (describiendo compuestos de la fórmula II), WO 00/09495, WO 00/27820, WO 00/59509, WO 98/11223, WO 00/27819, WO 01/55114, WO 01/58899 y EP 0 769 947, los cuales se describen por M. Prewett y otros en Cancer Research 59 (1999) 5209-5218, por F. Yuan y otros en Proc. Natl. Acad. Sci. USA, vol. 93, pág. 14765-14770, Diciembre de 1996, por Z. Zhu y otros en Cancer Res. 58, 1998, 3209-3214, y por J. Mordenti y otros en Toxicologic Pathology, Vol. 27, No. 1, pág. 14-21, 1999, aquellos que genérica y específicamente se describen en WO 00/37502 y WO 94/10202; y aquellos que se describen por M. S. O'Reily y otros, Cell 79, 1994, 315-328 (Angiostain™) y por M. S. O'Reily y otros, Cell 88, 1997, 277-285 (Endostain™), en cada caso, en particular en las reivindicaciones de compuesto, las preparaciones farmacéuticas y los productos finales de los ejemplos de trabajo, la material objeto de todo esto se incorpora aquí por referencia. Asimismo están comprendidos los estereoisómeros correspondientes así como las modificaciones de cristal correspondientes, por ejemplo, solvatos y

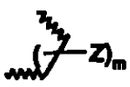
polimorfismos, los cuales se describen ahí. Los compuestos usados como ingredientes activos en las combinaciones aquí descritas pueden ser preparados y administrados como se describe en los documentos citados, respectivamente.

El término "PTK787" como se utiliza aquí, representa un compuesto de la fórmula II:



(II)

en donde r, n y m son cada uno 0, R_1 y R_2 juntos forman un puente de la fórmula II*,



(II*)

A, B, D y E son cada uno CH, G es metileno, X es imino, Y es 4-clorofenilo, y los enlaces caracterizados por una línea ondulado son dobles enlaces, descritos en, por ejemplo, el Ejemplo 38 de WO 98/35958. De preferencia, dicho compuesto es empleado en la forma de sus sales succinatos. Este fármaco o su sal puede ser administrado en, por ejemplo, la forma como se describe en la solicitud de patente de PCT citada.

Los "inhibidores de metaloproteinasa, como se define aquí, son, por ejemplo, Marimastat (BB-2516), Prinomastat (AG3340), Bay

12-9566, BMS-27591, MM1270B y Metastat (NSC 683551).

El término "otros compuestos que tienen un efecto vasculoestático" como se define aquí, se refiere en particular a los compuestos EMD-121974, doxorubicin, pacitaxel, IM-862, Thalidomida®, Linomida®, PKC412, AGM-1478, Suramin, y polisulfato de Pentosan.

Los derivados de epotilona de la fórmula I, en donde A representa O u NR_N, en donde R_N es hidrógeno o alquilo inferior, R es hidrógeno o alquilo inferior y Z es O, o un enlace, y los métodos para la preparación de dichos derivados de epotilona en particular son genérica y específicamente descritos en las patentes y solicitudes de patente WO 93/10121, patente de E. U. A. 6,194,181, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 y WO 00/31247, en cada caso, en particular, en las reubicaciones de compuesto y los productos finales de los ejemplos de trabajo, la material objeto de los productos finales, las preparaciones farmacéuticas y las reivindicaciones se incorporan aquí en la presente solicitud por referencia a estas publicaciones. Asimismo están comprendidos los estereoisómeros correspondientes, así como las publicaciones de cristal correspondientes, por ejemplo, solvatos y polimorfismos, que se describen ahí. Los derivados de epotilona de la fórmula I, especialmente epotilona B, pueden ser administrados como parte de composiciones farmacéuticas que se describen en WO 99/39694.

La trasformación de epotilona B a la lactama correspondiente

se describe en el Esquema 21 (pág. 31, 32) y Ejemplo 3 de WO 99/02514 (págs. 48-50). La transformación de un compuesto de la fórmula I que es diferente de epotilona B a la lactama correspondiente puede lograrse análogamente. Los derivados de epotilona correspondientes de la fórmula I, en donde R_N es alquilo inferior, pueden ser preparados a través de métodos conocidos en la técnica tales como reacción de alquilación reductiva empezando del derivado de epotilona en donde R_N es hidrógeno.

Además, la estructura de los agentes activos mencionados aquí por nombre puede ser tomada de la edición real del compendio estándar "The Merck Index" o de bases de datos, por ejemplo, patentes internacionales (por ejemplo, IMS World Publications). Su contenido correspondiente se incorpora aquí por referencia. Cualquier experto en la técnica está totalmente capacitado, basándose en estas referencias, a fabricar y probar las indicaciones y propiedades farmacéuticas en modelos de prueba estándares, tanto in vitro como in vivo.

Los compuestos usados como patrones de combinación (a) y (b) descritos aquí pueden ser preparados y administrados como se describe en los documentos citados, respectivamente.

Se entenderá que las referencias a los patrones de combinación (a) y (b) pretenden también incluir las sales farmacéuticamente aceptables. Si estos patrones de combinación (a) y (b) tienen, por ejemplo, por lo menos un centro básico, estos pueden formar sales de adición de ácido. Las sales de adición de

ácido correspondientes también pueden ser formadas teniendo, si se desea, un centro básico adicionalmente presente. Los patrones de combinación (a) y (b) que tienen un grupo ácido (por ejemplo, COOH) también pueden formar sales con bases. El patrón de combinación (a) o (b) o una sal farmacéuticamente aceptable del mismo también se puede utilizar en la forma de un hidrato o incluir otros solventes usados para cristalización.

Una combinación que comprende (a) un bisfosfonato, un compuesto en platino o un compuesto vasculoestático y (b) un derivado de epotilona de la fórmula I en donde A representa O o NR_N, en donde R_N es hidrógeno o alquilo inferior, R es hidrógeno o alquilo inferior, y Z es O o un enlace, en donde los ingredientes activos están presentes en cada caso en forma libre o en la forma de una sal farmacéuticamente aceptable y opcionalmente por lo menos un vehículo farmacéuticamente aceptable, será denominada de aquí en adelante como una combinación de la invención.

Las combinaciones de la invención inhiben el crecimiento de tumores sólidos, pero también de tumores líquidos. En una modalidad preferida de la invención, la enfermedad que será tratada es cáncer de próstata, en particular cáncer de próstata refractario de hormona con metástasis ósea. Además, una combinación de la invención que comprenda un compuesto vasculoestático, en particular PTK787, exhibe efectos benéficos en el tratamiento de enfermedades asociadas con angiogénesis desregulada.

La naturaleza de enfermedades proliferativas como

enfermedades de tumor sólido es multifactorial. Bajo ciertas circunstancias, se pueden obtener fármacos con diferentes mecanismos de acción. Sin embargo, considerando sólo cualquier combinación de fármacos que tengan un modo diferente de acción no necesariamente conducen a combinaciones con efectos ventajosos.

Todo lo más sorprendente es el hallazgo experimental que in vivo, la administración de una combinación de la invención comparada con una monoterapia aplicando solamente uno de los ingredientes farmacéuticamente activos usados en la combinación de la invención da como resultado no solamente un efecto antiproliferativo, especialmente sinergístico, más benéfico, por ejemplo, con respecto al retraso de la progresión en la enfermedad proliferativa o con respecto a un cambio en el volumen del tumor, y/o un efecto especialmente sinergístico, más benéfico de evitar eventos relacionados con el esqueleto (SREs), sino que también efectos benéficos sorprendentes adicionales, por ejemplo, menos efectos laterales y una mortalidad y morbidez reducidas. Además, dependiendo del tipo de tumor y la combinación particular usada, se puede obtener una reducción del volumen de tumor cuando se utiliza una combinación de la invención en casos en donde a través de monoterapia no se logra ninguna reducción del volumen del tumor. Las combinaciones de la invención también son adecuadas para evitar la diseminación metastática de tumores y el crecimiento o desarrollo de micrometástasis. La combinación de la invención en particular es adecuada para el tratamiento de pacientes con pobre

prognosis, es decir, en particular, en pacientes que no responden o recaen de un tratamiento anterior con un solo fármaco o una combinación diferente a la combinación de la invención.

Un beneficio adicional es que se puede utilizar dosis más bajas de los ingredientes activos de la combinación de la invención, por ejemplo, en donde las dosis necesariamente no solamente son más pequeñas sino que también se aplican con menos frecuencias, o se pueden utilizar con el fin de disminuir la incidencia de efectos laterales. Esto es de acuerdo con los deseos y requerimientos de los pacientes que serán tratados.

Se puede mostrar a través de modelos de prueba establecidos y en particular aquellos modelos de prueba descritos aquí que una combinación de la invención da como resultado los efectos benéficos descritos aquí anteriormente. Los expertos en la técnica pertinente están totalmente habilitados para seleccionar un modelo de prueba relevante para probar dichos efectos benéficos. La actividad farmacológica de una combinación de la invención puede ser, por ejemplo, demostrada en un estudio clínico o en un procedimiento de prueba como esencialmente se describe más adelante.

Los estudios clínicos adecuados, son en particular, estudios aleatorizados, doblemente ciegos, controlados por placebo paralelos. Dichos estudios son, en particular, adecuados para comparar los efectos de una monoterapia utilizando los ingredientes activos y una terapia utilizando una combinación de la invención, y para probar en particular el sinergismo de los ingredientes activos de las

combinaciones de la invención. Los efectos benéficos en las enfermedades proliferativas, por ejemplo, para evitar eventos relacionados con el esqueleto (SREs) en pacientes con cáncer de próstata con una historia de enfermedad ósea metastática, pueden ser determinados directamente a través de los resultados de estos estudios o través de cambios en el diseño de estudio que son conocidos para algún experto en la técnica. Los eventos SREs son definidos como eventos de fractura de huesos patológicos, eventos de compresión de médula espinal, cirugía de huesos, terapia con radiación en huesos y un cambio de terapia antineoplástica para tratar dolor de huesos. Preferiblemente, los eventos SREs son los puntos finales primarios de dichos estudios. Además, en tales estudios, el efecto sobre clasificaciones de dolor, uso analgésico, estado de funcionamiento, calidad de clasificaciones de vida, densidad mineral ósea, tiempo de progresión en huesos y progresión total, pueden ser evaluados.

En un diseño de estudio adecuado, los pacientes son aleatorizados en una forma doblemente ciega para recibir cada 3 semanas ya sea 2 mg de zoledronato intravenosamente como una infusión de 5 minutos o una infusión de 15 minutos, 4 mg de zoledronato intravenosamente como una infusión de 5 minutos o una infusión de 15 minutos, o un placebo intravenosamente como una infusión de 5 minutos o una infusión de 15 minutos, además de un compuesto de la fórmula I, por ejemplo, 6 ciclos de epotilona B, en donde cada ciclo consiste de entre 2.5 mg/m^2 y 6 mg/m^2 de epotilona

B administrada con un bolo de 5 minutos una vez a la semana durante 3 semanas seguido por 14 días restantes.

En otro diseño de estudio adecuado, los pacientes son aleatorizados en una forma doblemente ciega para recibir cada 2 semanas 45 mg de oxaliplatino/m^2 de superficie del cuerpo intravenosamente con una infusión de 2 a 6 horas o un placebo correspondiente además de un compuesto de la fórmula I, por ejemplo, 6 ciclos de epotilona B, en donde cada ciclo consiste de 2.6 mg/m^2, de epotilona B administrada como un bolo de 5 minutos una vez a la semana durante 3 semanas seguido por 14 días más.

En un diseño de estudio adecuado adicional, los pacientes son aleatorizados en una forma doblemente ciega para recibir diariamente, por ejemplo, 250 o 500 mg de PTK787 o un placebo correspondiente además un compuesto de la fórmula I, por ejemplo, 6 ciclos de epotilona B, en donde cada ciclo consiste de 2.5 mg/m^2 de epotilona B administrada como un bolo de 5 minutos una vez a la semana durante 3 semanas seguido por 14 días restantes.

En otro diseño de estudio, se aplicaron dosis semanales de 0.5 mg/m^2, 1.0 mg/m^2, 1.5 mg/m^2, 2.0 mg/m^2 o 2.5 mg/m^2, de epotilona B como una infusión intravenosa durante 5 minutos y se dosificó cisplatino por líneas de guía estándares, es decir, en una dosis semanal de 20-100 mg/m^2, de área de superficie del cuerpo, por ejemplo, 30 mg/m^2 semanalmente. La inyección de cisplatino se diluyó antes de la administración y se administró inmediatamente después de epotilona B como una infusión intravenosa de una hora.

Un ciclo de tratamiento consiste de la administración a los fármacos durante 3 semanas seguido por una semana restante.

Es un objeto de esta invención proporcionar una composición farmacéutica que comprenda una cantidad, que sea conjunta y terapéuticamente efectiva contra una enfermedad proliferativa, que comprenda una combinación de la invención. En esta composición, los patrones de combinación (a) y (b) pueden ser administrados conjuntamente, uno después del otro o en forma separada en una forma de dosis unitaria combinada o en dos formas de dosis unitarias separadas. La forma de dosis unitaria también puede ser una combinación fija.

Las composiciones farmacéuticas de acuerdo con la invención pueden ser preparadas en una forma conocida per se y son aquellas adecuadas para administración enteral, tal como administración oral o rectal, y administración parenteral a mamíferos (animales de sangre caliente), incluyendo seres humanos, que comprende una cantidad terapéuticamente efectiva de por lo menos un patrón de combinación farmacológicamente activo solo o en combinación con uno o más portadores farmacéuticamente aceptables, especialmente adecuados para aplicación enteral o parenteral.

La composición farmacéutica novedosa contiene, por ejemplo, de aproximadamente 10% a aproximadamente 100%, de preferencia de aproximadamente 20% a aproximadamente 60% de los ingredientes activos. Las preparaciones farmacéuticas para la terapia de combinación para administración enteral o parenteral son,

por ejemplo, aquellas en formas de dosis unitaria, tales como tabletas cubiertas con azúcar, tabletas, cápsulas o supositorios, y además ampolletas. Sino se indica de otra manera, se pueden preparar en una forma conocida per se, por ejemplo, a través de procedimientos de mezclado, granulación, recubrimiento con azúcar, disolución o liofilización convencionales. Se apreciará que el contenido unitario de un patrón de combinación contenido en una dosis individual de cada forma de dosis no necesita por si mismo constituir una cantidad efectiva, ya que la cantidad efectiva necesaria puede ser alcanzada a través de la administración de una pluralidad de unidades de dosis.

Para preparar las composiciones para forma de dosis oral, se pueden enviar cualquiera de los medios farmacéuticos usuales, tales como, por ejemplo, agua, glicoles, aceites, alcoholes, agentes saborizantes, conservadores, agentes colorantes; o vehículos tales como almidones, azúcares, celulosa microcristalina, diluyentes, agentes de granulación, lubricantes, aglutinantes, agentes de desintegración y similares, en el caso de preparaciones sólidas orales tales como, por ejemplo, polvos, cápsulas y tabletas, o las preparaciones orales sólidas siendo preferidas con respecto a las preparaciones líquidas. Debido a su facilidad de administración, las tabletas y las cápsulas representan la forma de dosis unitaria oral más ventajosa en donde obviamente se pueden emplear vehículos o farmacéuticos sólidos.

En particular, una cantidad terapéuticamente efectiva de cada

uno de los patrones de combinación de la combinación de la invención puede ser administrada simultánea o secuencialmente y en cualquier orden, y los componentes pueden ser administrados en forma separada o como una combinación fija. Por ejemplo, el método de retraso de progresión o tratamiento de una enfermedad proliferativa de acuerdo con la invención puede comprender (i) la administración del primer patrón de combinación en una forma de sal libre o farmacéuticamente aceptable, y (ii) la administración del segundo patrón de combinación en forma libre o de sal farmacéuticamente aceptable, simultánea o secuencialmente en cualquier orden, en cantidades conjunta y terapéuticamente efectivas, de preferencia en cantidades sinergísticamente efectivas, por ejemplo, en dosis diarias que corresponden a las cantidades descritas aquí. Los patrones de combinación individuales de la combinación de la invención pueden ser administrados en forma separada en diferentes momentos durante el curso de la terapia o concurrentemente en formas de combinación divididas o individuales. Además, el término administrar también abarca el uso de un profármaco de un patrón de combinación que se convierte in vivo al patrón de combinación como tal. La presente invención, por lo tanto, se debe entender que abarca todos estos regímenes de tratamiento simultáneo o alternante y el término "administrar" debe ser interpretado así por consiguiente.

La dosis efectiva de cada uno de los patrones de combinación empleados en la combinación de la invención puede variar

dependiendo del compuesto particular o la composición farmacéutica empleada, el modo de administración, la condición que va a ser tratada, la severidad de la condición que se va a tratar. De esta manera, el régimen de dosis en la combinación de la invención se selecciona de acuerdo con una variedad de factores, incluyendo la ruta de administración y la función renal y hepática del paciente. Un médico, clínico o veterinario experto en la técnica fácilmente puede determinar y prescribir la cantidad efectiva de los ingredientes activos individuales requeridos para evitar, contrarrestar o encontrar el progreso de la condición. La precisión óptima para lograr la concentración de los ingredientes activos dentro de la escala que produce eficacia sin toxicidad requiere de un régimen basándose en la cinética de la disponibilidad de los ingredientes activos para los sitios objetivo. Este involucra una consideración de la distribución, equilibrio y eliminación de los ingredientes activos.

Si el animal de sangre caliente es un ser humano, la dosis de un compuesto de la fórmula I preferiblemente está en la escala de aproximadamente 0.25 a 75, de preferencia de 0.5 a 50, por ejemplo, 2.5 mg/m^2 una vez a la semana durante 2 a 4, por ejemplo, 3 semanas, seguido por 6 a 8 días en el caso del paciente adulto.

La epotilona B de preferencia se administra en una dosis que se calcula de acuerdo con la fórmula III:

$$\text{dosis individual (mg/m2)} = (0.1 \text{ a } y) \times N \qquad \text{(III)}$$

en donde N es el número de semanas entre tratamientos e y es 6, en donde la epotilona B se administra en más de un ciclo de tratamiento

después de un intervalo de 1 semana a 6 semanas después del tratamiento precedente.

En una modalidad preferida de la invención, la epotilona B se administra semanalmente en una dosis que es de entre aproximadamente 0.1 a 6 mg/m^2, de preferencia de entre 0.1 y 3 mg/m^2, por ejemplo, 2.5 o 3.0 mg/m^2, durante 3 semanas después de un intervalo de 1 a 6 semanas, especialmente un intervalo de 1 semana, después del tratamiento precedente. En otra modalidad de la invención, dicha epotilona B de preferencia se administra a un ser humano cada 18 a 24 días en una dosis que es de entre aproximadamente 0.3 y 12 mg/m^2.

A menos que se especifique otra cosa, los bisfosfonatos descritos aquí pueden ser administrados en las siguientes dosis:

El ácido alendrónico puede ser administrado a un ser humano en una escala de dosis que varía de aproximadamente 5 a 10 mg/día.

El ácido clodrónico puede ser administrado a un ser humano, por ejemplo, en una escala de dosis que varía de aproximadamente 750 a 1500 mg/día.

El ácido etridónico puede ser administrado a un ser humano en una escala de dosis que varía de aproximadamente 200 a 400 mg/día.

El ácido ibandrónico puede ser administrado a un ser humano en una escala de dosis que varía de aproximadamente 1 a aproximadamente 4 mg cada 3 a 4 semanas.

El ácido risedrónico puede ser administrado a un ser humano

en una escala de dosis que varía de aproximadamente 20 a 30 mg/día.

El ácido pamidrónico puede ser administrado a un ser humano en una escala de dosis que varía de aproximadamente 15 a 90 mg cada 3 a 4 semanas.

El ácido tiludrónico puede ser administrado a un ser humano en una escala de dosis que varía de aproximadamente 200 a 400 mg/día.

El ácido zoledrónico puede ser administrado a un ser humano en una escala de dosis que varía de aproximadamente 2 a 10 mg, especialmente 4 u 8 mg, como una infusión intravenosa cada 3 semanas.

El carboplatino puede ser administrado intravenosamente a un ser humano en una escala de dosis que varía de aproximadamente 100 a 4000, por ejemplo, 200 mg/m^2 de superficie del cuerpo aproximadamente cada 4 a 6 semanas.

El oxaliplatino puede ser administrado intravenosamente a un ser humano en una escala de dosis que varía de aproximadamente 25 a 135, por ejemplo, 45 u 85 mg/m^2 de la superficie del cuerpo aproximadamente cada 2 a 3 semanas.

El cisplatino puede ser administrado a un ser humano en una escala de dosis que varía de aproximadamente 25 a 100 mg/m^2 aproximadamente cada 3 semanas.

Si el animal de sangre caliente es un ser humano, la dosis de PTK 187 de preferencia está en la escala de aproximadamente 50 a

1500, preferiblemente de aproximadamente 100 a 750, y muy preferiblemente de 250 a 500 mg/día.

En una modalidad preferida de la invención, la combinación de la invención comprende bisfosfonato seleccionado de ácido etridónico, ácido clodrónico, ácido tiludrónico, ácido pamidrónico, ácido alendrónico, ácido ibandrónico, ácido risedrónico y, muy preferiblemente, ácido zoledrónico.

En otra modalidad de la invención, la combinación de la invención comprende cisplatino, oxaliplatino o carboplatino.

En otra modalidad de la invención, la combinación de la invención comprende un vasculoestático de la fórmula II:

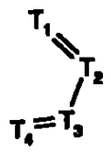
en donde r es de 0 a 2, n es 0 a 2, m es 0 a 4,

R_1 y R_2 son (i) alquilo inferior o

(ii) juntos forman un puente en la subfórmula II*,

la unión siendo lograda a través de los dos átomos de carbono terminales, o

(iii) juntos forman un puente en la subfórmula II**



(II**)

en donde uno o dos de los miembros de anillo T_1, T_2, T_3 y T_4 son nitrógeno y los otros en cada caso son CH, y la unión se logra a través de T_1 y T_4;

A, B, D y E son, independientemente uno del otro, N o CH, con la estimulación de que no más de dos estos radicales son N;

G es alquileno inferior, alquileno inferior substituido por aciloxi o hidroxi, $-CH_2-O$, $-CH_2-S-$, $-CH_2-NH-$, oxa (-O-), thia (-S-), o imino (-NH-);

Q es alquilo inferior;

R es H o alquilo inferior;

X es imino, oxa, o tia;

Y es arilo no substituido o substituido, piridilo, o cicloalquilo substituido o no substituido; y

Z es amino, amino mono o disubstituido, halógeno, alquilo, alquilo substituido, hidroxi, hidroxi eterificado o esterificado, nitro, ciano, carboxi, carboxi esterificado, alcanoilo, carbamoilo, carbamoilo N-mono o N,N-disubstituido, amidino, guanidino, mercapto, sulfo, feniltio, fenil-alquiltio inferior, alquilfeniltio, fenilsulfonilo, fenilo-alquilsulfinilo inferior, o alquilfenilsulfinilo, los substituyentes Z siendo iguales o diferentes uno del otro si más de un radical Z está presente;

en donde los enlaces se caracterizan, si están presentes, por una línea ondulada y son enlaces ya sea individuales o dobles;

o un N-óxido del compuesto definido, en donde uno o más átomos N lleva un átomo de oxígeno, o la sal de dicho compuesto teniendo por lo menos un grupo formador de sal. De preferencia, el compuesto de la fórmula II que será empleado es PTK787.

Los términos utilizados para la definición del compuesto de la fórmula II tienen los significados definidos en WO 98/35958, dichas definiciones se incluyen aquí por referencia.

En el compuesto de la fórmula I, preferiblemente A representa O. R es alquilo inferior, por ejemplo, etilo o muy preferiblemente metilo. Z de preferencia es O.

La combinación de la invención puede ser una preparación combinada o una composición farmacéutica.

Además, la presente invención se refiere a un método para tratar a un animal de sangre caliente que tenga una enfermedad proliferativa, en particular cáncer de próstata, especialmente cáncer próstata o refractario de horma con metástasis ósea, que comprende administrar al animal una combinación de la invención en una cantidad que es conjunta y terapéuticamente efectiva contra una enfermedad proliferativa, en donde los patrones de combinación también pueden estar presentes en la forma de sales farmacéuticamente aceptables.

Además, la presente invención se refiere al uso de una combinación de la invención para el retraso de la progresión o el tratamiento de una enfermedad proliferativa y para la preparación de un medicamento para el retraso de la progresión o tratamiento de una enfermedad proliferativa.

Además, la presente invención se refiere al uso de un bisfosfonato, un compuesto de platino o un compuesto vasculoestático en combinación con un derivado de epotilona de la fórmula I, en donde el compuesto A representa O u NR_N, en donde R_N es hidrógeno o alquilo inferior, R es hidrógeno o alquilo inferior, y Z es O, o un enlace, para la preparación de un medicamento para el

retraso de la progresión o tratamiento de una enfermedad proliferativa.

Además, la presente invención proporciona el paquete comercial que comprende como ingredientes activos la combinación de la invención, junto las instrucciones para su uso simultáneo, separado o secuencial en el retraso de la progresión del tratamiento de una enfermedad proliferativa.

Los siguientes ejemplos ilustran la invención descrita anteriormente; sin embargo no pretenden limitar el alcance de la invención de ninguna manera. Los efectos benéficos de la combinación de la invención también pueden ser determinados a través de otros modelos de prueba conocidos como tales por aquellos expertos en la técnica.

EJEMPLO 1

Crecimiento de células de carcinoma de próstata humana PC-3MM2 entre la tibia en ratones pelados

Se inyectó una suspensión de célula (2×10^5 células) de la línea de carcinoma de próstata humana PC-3MM2 en la tibia de ratones pelados. El crecimiento del tumor en este modelo conduce a la destrucción del hueso que claramente es visible después de 4 semanas. El tratamiento con los compuestos se inició 7 días después de la inyección de las células tumorales. En ese momento, los animales fueron clasificados en grupos con escala media y equivalente de tamaños de tumor. El tratamiento después fue

aleatorizado a los diferentes grupos y tratados solamente con vehículos; con (a) un bisfosfonato, por ejemplo, ácido zoledrónico, un patrón de combinación (b), por ejemplo, epotilona B; o los patrones combinados (a) y (b), por ejemplo, ácido zoledrónico y epotilona B. El análisis después de 3-4 semanas de tratamiento incluye la estimación de la destrucción de hueso y la carga de un tumor.

EJEMPLO 2

Bisfosfonato y una epotilona en fragmento de tumor de carcinoma de próstata humana DU 145 desarrollado s.c. en ratones pelados

Los tumores de carcinoma de próstata humana DU 145 se desarrollaron s.c. en ratones pelados. Se implantaron subcutáneamente (s.c.) fragmentos de tumor (aproximadamente 25 mg cada uno) en el flanco izquierdo de ratones pelados. El tratamiento con los compuestos se inició cuando los tumores alcanzaron un tamaño de 80-100 mm^2 (usualmente después de 10-15 días). En ese momento, los animales fueron clasificados en grupos con escala media equivalente de tamaños de tumor. El tratamiento después fue aleatorizado a los diferentes grupos y tratado solamente con vehículos; con (a) un bisfosfonato, por ejemplo, ácido zoledrónico, un patrón de combinación (b), por ejemplo, epotilona B; o los patrones combinados (a) y (b), por ejemplo, ácido zoledrónico y epotilona B. El tamaño de tumor (medido con calibradores) y el peso

del cuerpo se analizaron cada 3-5 días.

EJEMPLO 3

Oxaliplatino y epotilona B en fragmentos de tumor de carcinoma de próstata humana DU 145 desarrollados s.c. en ratones pelados

Se desarrollaron s.c. tumores de carcinoma de próstata humana DU 145 en ratones pelados. Se implantaron subcutáneamente (s.c.) fragmentos de tumor (aproximadamente 25 mg cada uno) en el flanco izquierdo de ratones pelados. El tratamiento con los compuestos se inició cuando los tumores alcanzaron un tamaño de 80-100 mm^2 (usualmente después de 10-15 días). En ese momento, los animales fueron clasificados en grupos con escala media y equivalente de tamaños de tumor. El tratamiento después fue aleatorizado a los diferentes grupos y tratado solamente con vehículos; con (a) oxaliplatino; (b) epotilona B; o los patrones combinados (a) y (b), administrados ya sea simultáneamente o secuencialmente en cualquier orden. El tamaño de tumor (medido con calibradores) y el peso del cuerpo se analizaron cada 3-5 días.

EJEMPLO 4

Carboplatino y epotilona B en fragmentos de tumor de cáncer de pulmón humano NCI-H596 desarrollado s.c. en ratones pelados

En el mismo modelo como el utilizado en el Ejemplo 3, pero empleando la línea de célula de tumor de pulmón NCI-H596, se puede demostrar la eficacia superior de la combinación consistiendo

de carboplatino y epotilona B comparado con los fármacos individuales.

EJEMPLO 5

PTK787 y epotilona B en xenoinjertos subcutáneos de carcinoma de próstata humana DU 145 en ratones pelados

Se desarrollaron s.c. células de carcinoma de próstata humana DU 145 en ratones pelados. Se inyectaron subcutáneamente (s.c.) células tumorales (10^6) en los flancos izquierdo y derecho de ratones pelados. El tratamiento con los compuestos se inició después de 25-32 días cuando los tumores alcanzaron el tamaño de 80-100 mm^2. En ese momento, los animales fueron clasificados en grupos con escala media y equivalente de tamaños de tumor. El tratamiento después fue aleatorizado a los diferentes grupos y se trataron solamente con vehículos; con 2 mg/kg de epotilona B dada una vez a la semana intravenosamente; 50 mg/kg de PTK 787 administrada una vez al día p.o.; o los patrones combinados, epotilona B y PTK787. Los cambios en el tamaño de tumor y el peso del cuerpo se miden con calibradores en una base semanal. Los resultados muestran una inhibición aditiva del crecimiento de tumor sin la pérdida e incrementada concomitantemente del peso del cuerpo.

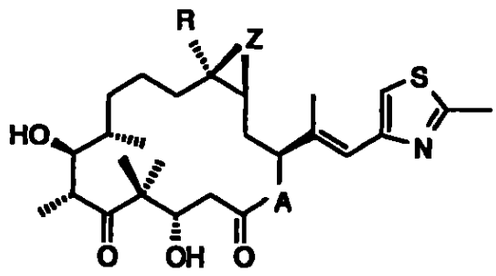
EJEMPLO 6

Epotilona B y PTK787 en xenoinjertos subcutáneo de melanoma de ratón singeneico B16 en ratones negros

Se inyectaron subcutáneamente (s.c.) células de melanoma de ratón B16 (5×10^4) en las orejas de ratones negros. El tratamiento con los compuestos se inició después de 7 días. En ese momento, los animales fueron clasificados en grupos con escala media y equivalente de tamaños de tumor. El tratamiento después fue aleatorizado a diferentes grupos y tratados solamente con vehículos; con epotilona B dada una vez a la semana intravenosamente; con PTK787 administrada una vez al día p.o.; o los patrones combinados, epotilona B y PTK787. Se verificó el crecimiento de tumor primario en una base semanal a través de análisis ayudado por computadora de imágenes fotográficas de melanomas. Los animales fueron necropsiados 3 semanas después de la iniciación del tratamiento. Se analizó la diseminación metastática pesando los nodos linfáticos cervicales.

REIVINDICACIONES

1.- Una combinación que comprende (a) un bisfosfonato, un compuesto de platino o un compuesto vasculoestático, y (b) un derivado de epotilona de la fórmula I:



(I)

en donde A representa O u NR_N, en donde R_N es hidrógeno o alquilo inferior, R es hidrógeno o alquilo inferior, y Z es O, o un enlace,

en donde los ingredientes activos (a) e (b) están presentes en cada caso en forma libre o en la forma de una sal farmacéuticamente aceptable y opcionalmente por lo menos un vehículo farmacéuticamente aceptable; para uso simultáneo, separado o secuencial.

2.- Una combinación de acuerdo con la reivindicación 1, que comprende (a) carboplatino, u oxaliplatino y (b) un derivado de epotilona de la fórmula I,

en donde A representa O u NR_N, en donde R_N es hidrógeno o alquilo inferior, R es hidrógeno o alquilo inferior, y Z es O, o un enlace,

en donde los ingredientes activos (a) e (b) están presentes en cada

caso en forma libre o en la forma de una sal farmacéuticamente aceptable y opcionalmente por lo menos un vehículo farmacéuticamente aceptable; para uso simultáneo, separado o secuencial.

3.- La combinación de acuerdo con la reivindicación 1, en donde se emplea un bisfosfonato seleccionado del grupo que consiste de ácido etridónico, ácido clodrónico, ácido tiludrónico, ácido pamidrónico, ácido alendrónico, ácido ibandrónico, ácido risedrónico y ácido zoledrónico.

4.- La combinación de acuerdo con la reivindicación 3, en donde el bisfosfonato es ácido zoledrónico.

5.- La combinación de acuerdo con la reivindicación 1, que comprende un compuesto vasculoestático.

6.- La combinación de acuerdo con la reivindicación 5, en donde el compuesto vasculoestático es PTK787.

7.- La combinación de acuerdo con cualquiera de las reivindicaciones 1 a 6, que comprende un derivado de epotilona de la fórmula I, en donde A representa O, R es alquilo inferior e hidrógeno y Z es O, o un enlace.

8.- La combinación de acuerdo con cualquiera de las reivindicaciones 1 a 7, la cual es una preparación combinada o una composición farmacéutica.

9.- Un método para tratar a un animal de sangre caliente que tiene una enfermedad proliferativa, el cual comprende administrar al animal una combinación de acuerdo con cualquiera de las

reivindicaciones 1 a 8 en una cantidad que es conjunta y terapéuticamente efectiva contra una enfermedad proliferativa en donde los compuestos también pueden estar presentes en la forma de sus sales farmacéuticamente aceptables.

10.- El método de tratamiento de acuerdo con la reivindicación 9, en donde se emplea un bisfosfonato y la enfermedad proliferativa es cáncer de próstata refractario de hormona con metástasis ósea.

11.- El método de tratamiento de acuerdo con la reivindicación 9, en donde se emplea carboplatino u oxaliplatino y la enfermedad proliferativa en cáncer de ovario, cáncer de pulmón, cáncer de cabeza o cuello, cáncer de cerviz, cáncer de próstata o cáncer de colon.

12.- El método de tratamiento de acuerdo con la reivindicación 9, en donde se emplea PTK787 y la enfermedad proliferativa es cáncer de ovario, cáncer de pulmón, cáncer de cabeza o cuello, cáncer de cerviz, cáncer de próstata o cáncer de colon.

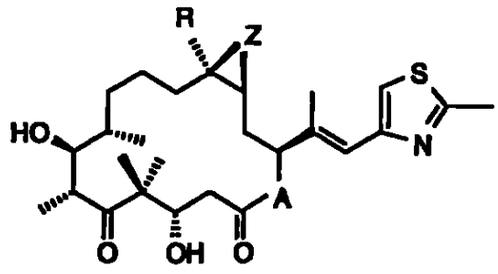
13.- Una composición farmacéutica que comprende una cantidad que es conjunta y terapéuticamente efectiva contra una enfermedad proliferativa de una combinación farmacéutica de acuerdo con cualquiera de las reivindicaciones 1 a 8, y por lo menos un vehículo farmacéuticamente aceptable.

14.- Una combinación de acuerdo con cualquiera de las reivindicaciones 1 a 8, para utilizarse en el retraso de la progresión o en el tratamiento de una enfermedad proliferativa.

15.- El uso de una combinación de acuerdo con cualquiera de

las reivindicaciones 1 a 8 para la preparación de un medicamento para el retraso de la progresión o para el tratamiento de una enfermedad proliferativa.

16.- El uso de un bisfosfonato en combinación con un derivado de epotilona de la fórmula I:

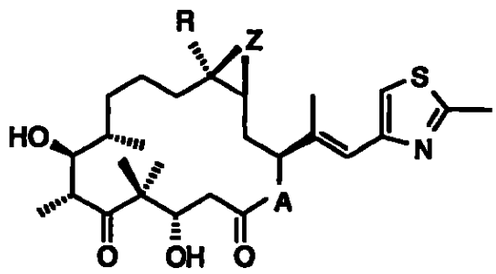


(I)

en donde el compuesto A representa O u NR_N, en donde R_N es hidrógeno o alquilo inferior, R es hidrógeno o alquilo inferior, y Z es O, o un enlace,

para la preparación de un medicamento para el retraso de la progresión o el tratamiento de una enfermedad proliferativa.

17.- El uso de cisplatino, carboplatino u oxaliplatino en combinación con un derivado de epotilona de la fórmula I:

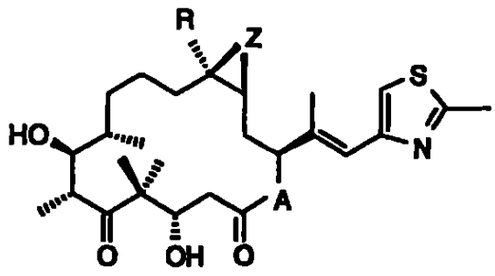


(I)

en donde el compuesto A representa O u NR_N, en donde R_N es hidrógeno o alquilo inferior, R es hidrógeno o alquilo inferior, y Z es O, o un enlace,

para la preparación de un medicamento para el retraso de la progresión o el tratamiento de una enfermedad proliferativa.

18.- El uso de un compuesto vasculoestático en combinación con un derivado de epotilona de la fórmula I:



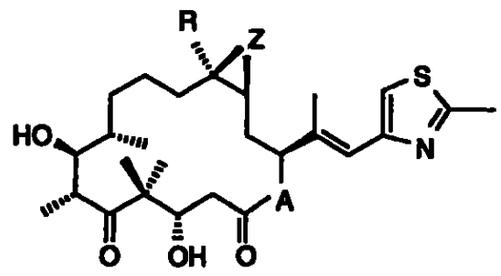
(I)

en donde A representa O u NR_N, en donde R_N es hidrógeno o alquilo inferior, R es hidrógeno o alquilo inferior, y Z es O, o un enlace,

para la preparación de un medicamento para el retraso de la progresión o el tratamiento de una enfermedad asociada con angiogénesis desregulada.

19.- El uso de acuerdo con la reivindicación 18, en donde el compuesto vasculoestático es PTK787.

20.- Un paquete comercial que comprende (a) un bisfosfonato, un compuesto de platino o un compuesto vasculoestático, y (b) un derivado de epotilona de la fórmula I:



(I)

en donde A representa O u NR_N, en donde R_N es hidrógeno o alquilo inferior, R es hidrógeno o alquilo inferior, y Z es O, o un enlace,

junto con las instrucciones para su uso simultáneo, separado o secuencial en el retraso de la progresión o en el tratamiento de una enfermedad proliferativa.

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 0 2 / 0 8 0 2 0

International Filing Date 18 07 2002 18 JUL 2002

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 4-32073A/078/079

Box No. I TITLE OF INVENTION

COMBINATIONS COMPRISING EPOTHILONES AND PHARMACEUTICAL USES THEREOF

Box No. II APPLICANT ☐ This person is also inventor

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

Novartis AG
Lichtstrasse 35
4056 Basel
CH

Telephone No. +41 61 324 11 11
Facsimile No. +41 61 322 75 32
Teleprinter No.
Applicant's registration No. with the Office

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

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

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

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

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

Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
Brunner Strasse 59
1230 Vienna
AT

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

Applicant's registration No. with the Office

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

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

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

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

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

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

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

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

Telephone No. +41 61 324 11 11
Facsimile No. +41 61 322 75 32
Teleprinter No.
Agent's registration No. with the Office

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

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.)*

CHEN, TianLing
38 Park Street, #18C
Florham Park, NJ 07932
US

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: US

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

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.)*

GREELEY, Diane
46 Lakeview Terrace
Watchung, NJ 07069
US

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: US

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

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.)*

ROTHERMEL, John David
46 School House Road
Randolph, NJ 07869
US

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: US

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

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.)*

WARTMANN, Markus
Kornfeldstrasse 14
4125 Riehen
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

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

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Sheet No. ...3...

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.)*

WOOD, Jeanette Marjorie
In den Kleematten 18
4105 Biel-Benken
CH

This person is:
- [ ] applicant only
- [x] 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: NZ

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 [x] 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

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

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

Applicant's registration No. with the Office

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

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

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

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

Box No. V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

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

Regional Patent

☐ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☐ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

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

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

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

☐	☐	☐ .....
☐	☐	☐ .....

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

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

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

(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. 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.

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

Box No. VI PRIORITY CLAIM

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

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 19 July 2001 (19.07.01)	60/306571	US		
item (2) 19 July 2001 (19.07.01)	60/306559	US		
item (3) 19 July 2001 (19.07.01)	60/306560	US		
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**	:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

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

request (including declaration sheets)	:	7
description (excluding sequence listing part)	:	18
claims	:	4
abstract	:	1
drawings	:	0
Sub-total number of sheets	:	30
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)*	:	0
Total number of sheets	:	30

(b) sequence listing part of description filed in computer readable form

(i) ☐ only (under Section 801(a)(i))

(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*: .....

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

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 36671 + 37586 ..... : 2
5. ☐ statement explaining lack of signature :
6. ☒ priority document(s) identified in Box No. VI as item(s): ..... : 3
7. ☐ translation of international application into *(language)*: ..... :
8. ☐ separate indications concerning deposited microorganism or other biological material :
9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))
   - (i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application) :
   - (ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter* :
   - (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column :
10. ☐ other *(specify)*: ..... :

Figure of the drawings which should accompany the abstract: —

Language of filing of the international application: 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

14.08.2002

GROS, Florent AV 36671 + 37586

For receiving Office use only

1. Date of actual receipt of the purported international application: 18 JUL 2002 18.07.02

2. Drawings:
   - ☐ received:
   - ☐ not received:

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

4. Date of timely receipt of the required corrections under PCT Article 11(2):

5. International Searching Authority (if two or more are competent): ISA /

6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

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

PATENT COOPERATION TREATY

PCT

From the RECEIVING OFFICE

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

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

(PCT Rule 20.5(c))

Date of mailing (day/month/year)	09.08.2002
Applicant's or agent's file reference: 4-32073A/078/079	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/EP 02/ 08020	18/07/2002	19/07/2001

Applicant: NOVARTIS AG

Title of the invention:

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

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

Name and mailing address of the Receiving Office	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	G. Most

Form PCT/RO/105 (Juli 1992)

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 January 2003 (30.01.2003)

PCT

(10) International Publication Number
WO 03/007924 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/EP02/08020

(22) International Filing Date: 18 July 2002 (18.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/306,571	19 July 2001 (19.07.2001)	US
60/306,559	19 July 2001 (19.07.2001)	US
60/306,560	19 July 2001 (19.07.2001)	US

(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-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H. [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CHEN, TianLing [US/US]; 38 Park Street, #18C, Florham Park, NJ 07932 (US). GREELEY, Diane [US/US]; 46 Lakeview Terrace, Watchung, NJ 07069 (US). ROTHERMEL, John, David [US/US]; 46 School House Road, Randolph, NJ 07869 (US). WARTMANN, Markus [CH/CH]; Kornfeldstrasse 14, CH-4125 Riehen (CH). WOOD, Jeanette, Marjorie [NZ/CH]; In den Kleematten 18, CH-4105 Biel-Benken (CH).

(74) Agent: GROS, Florent; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).

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

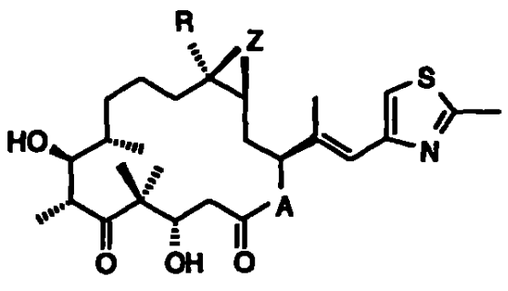
(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR).

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.

(54) Title: COMBINATIONS COMPRISING EPOTHILONES AND PHARMACEUTICAL USES THEREOF



(I)

(57) Abstract: The invention relates to a combination which comprises (a) a bisphosphonate, a platinum compound or a vasculostatic compound and (b) an epothilone derivative of formula (I), wherein A represents O or NR_N, wherein R_N is hydrogen or lower alkyl, R is hydrogen or lower alkyl, and Z is O or a bond, in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use, in particular for the delay of progression or treatment of a proliferative disease, especially a solid tumor disease; a pharmaceutical composition, a commercial package or product comprising such a combination; the use of such a combination for the preparation of a medicament for the delay of progression or treatment of a proliferative disease and to a method of treatment of a warm-blooded animal.

WO 03/007924 A2

(12) INTERNATIONAL APPLICATI N PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 January 2003 (30.01.2003)

PCT

(10) International Publication Number
WO 03/007924 A3

(51) International Patent Classification⁷: A61P 35/00, A61K 31/427, 31/282, 33/24, 31/4439, 31/663

(21) International Application Number: PCT/EP02/08020

(22) International Filing Date: 18 July 2002 (18.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/306,571 19 July 2001 (19.07.2001) US
60/306,559 19 July 2001 (19.07.2001) US
60/306,560 19 July 2001 (19.07.2001) US

(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*): CHEN, TianLing [US/US]; 38 Park Street, #18C, Florham Park, NJ 07932 (US). GREELEY, Diane [US/US]; 46 Lakeview Terrace, Watchung, NJ 07069 (US). ROTHERMEL, John, David [US/US]; 46 School House Road, Randolph, NJ 07869 (US). WARTMANN, Markus [CH/CH]; Kornfeldstrasse 14, CH-4125 Riehen (CH). WOOD, Jeanette, Marjorie [NZ/CH]; In den Kleematten 18, CH-4105 Biel-Benken (CH).

(74) Agent: GROS, Florent; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).

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

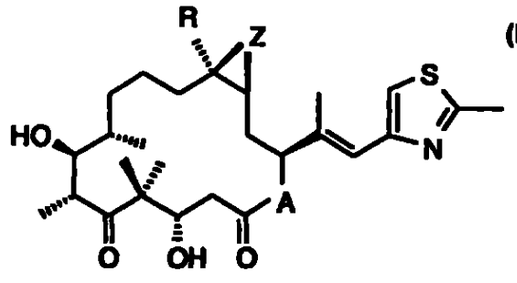
(84) Designated States (*regional*): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR).

Published:
— *with international search report*

(88) Date of publication of the international search report:
25 September 2003

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.

(54) Title: COMBINATIONS COMPRISING EPOTHILONES AND PHARMACEUTICAL USES THEREOF



(I)

(57) Abstract: The invention relates to a combination which comprises (a) a bisphosphonate, a platinum compound or a vasculostatic compound and (b) an epothilone derivative of formula (I), wherein A represents O or NR_N, wherein R_N is hydrogen or lower alkyl, R is hydrogen or lower alkyl, and Z is O or a bond, in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use, in particular for the delay of progression or treatment of a proliferative disease, especially a solid tumor disease; a pharmaceutical composition, a commercial package or product comprising such a combination; the use of such a combination for the preparation of a medicament for the delay of progression or treatment of a proliferative disease and to a method of treatment of a warm-blooded animal.

WO 03/007924 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/08020

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P35/00 A61K31/427 A61K31/282 A61K33/24 A61K31/4439 A61K31/663

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 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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 00485 A (SCHERING AG) 6 January 2000 (2000-01-06)	1,2,5, 7-9,11, 13-18,20
A	page 4-5; claims 1-6,8-10 page 8, line 13-18 page 42-43	12
X	WO 00 49019 A (SCHERING AG) 24 August 2000 (2000-08-24)	1,2,5, 7-9,11, 13-18,20
A	page 2-4; claims 1,5 page 6, line 32-38 page 19, line 21,22 page 24-25	12

-/-

[X] Further documents are listed in the continuation of box C. [X] 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
12 June 2003	23. 06. 2003

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	Kanbier, D

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 18439 A (SCHERING AG) 6 April 2000 (2000-04-06)	1,2,5, 7-9,11, 13-15, 17,18,20
A	page 4-5; claims 1,2,13,15,22 page 9-10	6,12,19
X	WO 99 39694 A (NOVARTIS ERFIND VERWALT GMBH) 12 August 1999 (1999-08-12) cited in the application	1,5,7-9, 13-15, 18,20
Y	page 1, line 21-24; claim 1	1,3,4, 7-10, 13-16,20
A	page 4, line 9-11 page 11, line 20-34 page 12, line 10-31	12
Y	STEARNS M E ET AL: "EFFECTS OF ALENDRONATE AND TAXOL ON PC-3 ML CELL BONE METASTASES INSCID MICE" INVASION METASTASIS, S. KARGER, BASEL, CH, vol. 16, no. 3, 1996, pages 116-131, XP000946388 ISSN: 0251-1789 page 127-129 page 117, right-hand column page 117, right-hand column, paragraph 2 -page 118, left-hand column, paragraph 1	3,7-10, 13-16,20
X	FR 2 775 187 A (NOVARTIS AG) 27 August 1999 (1999-08-27) example 3; table 3	1,5,7-9, 11, 13-15, 17,18,20
Y	page 11, line 22-27; tables 6,8,9 page 12, line 19-35; claims 1,13,16 page 13, line 23-26 page 15, line 19-29 page 20, line 20 -page 21, line 2	3,7-10, 13-16,20
Y	WO 00 59485 A (NOVARTIS ERFIND VERWALT GMBH; NOVARTIS AG) 12 October 2000 (2000-10-12) page 1, paragraphs 2,3; claims 1,5,7 page 2, paragraphs 3,4 page 3, paragraph 3 page 4, paragraphs 3,6 page 23, paragraphs 2,3	1,3,4, 7-10, 13-16,20
Y	WO 00 71104 A (NOVARTIS ERFIND VERWALT GMBH; NOVARTIS AG) 30 November 2000 (2000-11-30) page 2, paragraph 4; claims 1,6 page 7, paragraph 6	1,3,4, 7-10, 13-16,20

-/—

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/08020

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	YANO ET AL: "Treatment for malignant pleural effusion of human lung adenocarcinoma by inhibition of vascular endothelial growth factor receptor tyrosine kinase phosphorylation" CLINICAL CANCER RESEARCH, vol. 6, no. 3, 2000, pages 957-965, XP001151899 page 964	1,5,6,8, 9,12-15, 18-20
P,X	SEIDEN, MICHAEL V.: "Ovarian cancer" ONCOLOGIST (2001), 6(4), 327-332 , XP001159112 page 332, right-hand column	1,5,7-9, 13-15, 18,20

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 49295 A (UNIV CALIFORNIA) 12 July 2001 (2001-07-12) page 2, line 31,32 page 4-5; claims 1,2,8,25	1,3,4, 7-10, 13-16,20
A	DIEL I J ET AL: "REDUCTION IN NEW METASTASES IN BREAST CANCER WITH ADJUVANT CLODRONATE TREATMENT" NEW ENGLAND JOURNAL OF MEDICINE, THE, MASSACHUSETTS MEDICAL SOCIETY, WALTHAM, MA, US, vol. 339, no. 6, 6 August 1998 (1998-08-06), pages 357-363, XP009005011 ISSN: 0028-4793 page 357-8	1
X	WO 99 01124 A (SLOAN KETTERING INST CANCER) 14 January 1999 (1999-01-14) page 2, line 32-36; claims 1-6,46,47,50	1,5,7-9, 13-15, 18,20
Y	page 33, line 12-17; table 4	1,5,6,8, 9,12-15, 18-20
X	WO 99 02514 A (SQUIBB BRISTOL MYERS CO) 21 January 1999 (1999-01-21) cited in the application page 8, line 20 -page 9, line 17	1,5,7-9, 13-15, 18,20
Y	page 10, line 10-29; claims 1,4,5; examples 3,5-7	1,5,6,8, 9,12-15, 18-20
Y	WOOD J M ET AL: "PTK787/ZK 222584, A NOVEL AND POTENT INHIBITOR OF VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR TYROSINE KINASES, IMPAIRS VASCULAR ENDOTHELIAL GROWTH FACTOR-INDUCED RESPONSES AND TUMOR GROWTH AFTER ORAL ADMINISTRATION" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 60, no. 8, 15 April 2000 (2000-04-15), pages 2178-2189, XP000971163 ISSN: 0008-5472 page 2187; figures 8,9; table 2 page 2183, left-hand column, paragraph 3 -page 2184, left-hand column, paragraph 2	1,5,6,8, 9,12-15, 18-20

-/—

International Application No. PCT/EP 02 08020

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 3, 4, 10, 16; partly 1, 7-9, 13-15, 20

   Combinations of Epothilone derivatives of formula (I) with bisphosphonates, for use in treatments of proliferative diseases

2. Claims: 2, 11, 17; partly 1, 7-9, 13-15, 20

   Combinations of Epothilone derivatives of formula (I) with platinum compounds, for use in treatments of proliferative diseases.

3. Claims: 12, 18, 19; partly 1, 5-9, 13-15, 20

   Combinations of Epothilone derivatives of formula (I) with vasculostatic compounds, for use in treatments of proliferative diseases and diseases associated with deregulated angiogenesis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/08020

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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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:

see additional sheet

1. [X] 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.

[X] No protest accompanied the payment of additional search fees.

12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/08020

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0000485 A	06-01-2000	DE 19830060 A1	10-02-2000
		DE 19923001 A1	16-11-2000
		AU 5036999 A	17-01-2000
		WO 0000485 A1	06-01-2000
WO 0049019 A	24-08-2000	DE 19908760 A1	24-08-2000
		AU 3804800 A	04-09-2000
		WO 0049019 A2	24-08-2000
WO 0018439 A	06-04-2000	DE 19845798 A1	13-04-2000
		AU 1264200 A	17-04-2000
		WO 0018439 A2	06-04-2000
WO 9939694 A	12-08-1999	AU 753519 B2	17-10-2002
		AU 2722699 A	23-08-1999
		BE 1012140 A3	02-05-2000
		BR 9907647 A	14-11-2000
		CA 2320182 A1	12-08-1999
		CN 1292683 T	25-04-2001
		WO 9939694 A2	12-08-1999
		EP 1052974 A2	22-11-2000
		FR 2774909 A1	20-08-1999
		HU 0101564 A2	28-11-2001
		IT MI990208 A1	05-08-1999
		JP 2002502810 T	29-01-2002
		NO 20003930 A	04-10-2000
		PL 342629 A1	18-06-2001
		SK 11702000 A3	18-01-2001
		TR 200002299 T2	21-11-2000
		TW 457095 B	01-10-2001
		ZA 9900874 A	05-08-1999
FR 2775187 A	27-08-1999	AU 755944 B2	02-01-2003
		AU 2927999 A	15-09-1999
		BE 1011980 A5	07-03-2000
		CA 2319752 A1	02-09-1999
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		FR 2775187 A1	27-08-1999
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		US 2002028839 A1	07-03-2002
WO 0059485 A	12-10-2000	AU 4543500 A	23-10-2000
		WO 0059485 A2	12-10-2000
		EP 1165139 A2	02-01-2002
		JP 2002541096 T	03-12-2002
		US 2002061866 A1	23-05-2002
WO 0071104 A	30-11-2000	AU 5214100 A	12-12-2000
		BR 0010808 A	27-08-2002
		CA 2374049 A1	30-11-2000
		CN 1384749 T	11-12-2002
		WO 0071104 A2	30-11-2000
		EP 1178810 A2	13-02-2002
		HU 0201329 A2	28-08-2002
		JP 2003500352 T	07-01-2003

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1, 7-10, 13-16, 20 relate to compositions, methods and uses involving an extremely large number of possible compounds by way of the term "bisphosphonates".
Likewise, present claims 1, 7-10, 13-15, 20 relate to compositions, methods and uses involving an extremely large number of possible compounds by way of the term "platinum compound".
Due thereto, a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search over the complete scope of the claims impossible.

Furthermore, present claims 1, 5, 7-10, 13-15, 18, 20 relate to compositions, methods and uses involving a compound defined by reference to a desirable characteristic or property, namely:
having a vasculostatic effect.
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a limited number of such compounds.
In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). A compound cannot be sufficiently defined by its mechanism of action in vivo and/or its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), supported and disclosed, namely those parts relating to the compounds specifically claimed in the appropriate claim(s) and used in the appropriate example(s).

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

Information on patent family members

International Application No
PCT/EP 02/08020

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0071104 A		NO 20015638 A	15-01-2002
		NZ 515541 A	28-03-2003
		SK 16682001 A3	04-04-2002
		US 2002142996 A1	03-10-2002
WO 0149295 A	12-07-2001	AU 2756701 A	16-07-2001
		CA 2396393 A1	12-07-2001
		EP 1267888 A1	02-01-2003
		WO 0149295 A1	12-07-2001
		US 2003027211 A1	06-02-2003
WO 9901124 A	14-01-1999	AU 756699 B2	23-01-2003
		AU 5792998 A	25-01-1999
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		WO 9901124 A1	14-01-1999
		US 6204388 B1	20-03-2001
		US 6316630 B1	13-11-2001
		US 6300355 B1	09-10-2001
		US 6369234 B1	09-04-2002
		US 6284781 B1	04-09-2001
		US 2002002194 A1	03-01-2002
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		ZA 9711282 A	09-02-1999
WO 9902514 A	21-01-1999	AU 731497 B2	29-03-2001
		AU 7972098 A	08-02-1999
		BG 104068 A	29-09-2000
		BR 9810555 A	15-08-2000
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		EE 200000013 A	15-08-2000
		EP 1019389 A2	19-07-2000
		HU 0103111 A2	29-04-2002
		JP 2002512634 T	23-04-2002
		LT 99153 A ,B	25-08-2000
		LV 12569 A	20-11-2000
		LV 12569 B	20-04-2001
		NO 20000076 A	07-01-2000
		NZ 501198 A	28-09-2001
		PL 338003 A1	25-09-2000
		SK 181799 A3	06-08-2001
		TR 200000065 T2	21-11-2000
		WO 9902514 A2	21-01-1999
		ZA 9805938 A	10-01-2000

PATENT COOPERATION TREATY

Corporate Intellectual Property
26. Juni 2003
APPL | M/D | F/L | PS | Copy:

23.08.2003
4-32073A/078/079
James Stuttle

VT
PCT
EP02/08020

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

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

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 4-32073A/078/079	Date of mailing (day/month/year) 23/06/2003
International application No. PCT/EP 02/ 08020	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant NOVARTIS AG	International filing date (day/month/year) 18/07/2002

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

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

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

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

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

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

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

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

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

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

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

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

   Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Sylvia Hermier

Form PCT/ISA/220 (July 1998)

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? 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?

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.

NOTES TO FORM PCT/ISA/220 (continued)

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

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

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

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

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

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

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

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

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

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

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

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

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

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

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, 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.

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 Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
4-32073A/078/079		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 02/08020	18/07/2002	19/07/2001
Applicant		
NOVARTIS AG		

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

This International Search Report consists of a total of 10 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, 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 readble 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. [X] Certain claims were found unsearchable (See Box I).

3. [X] Unity of invention is lacking (see Box II).

4. With regard to the title,

   [X] the text is approved as submitted by the applicant.

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

5. With regard to the abstract,

   [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 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.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/08020

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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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:

see additional sheet

1. [X] 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.

[X] No protest accompanied the payment of additional search fees.

International Application No. PCT/EP 02 08020

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 3, 4, 10, 16; partly 1, 7-9, 13-15, 20

   Combinations of Epothilone derivatives of formula (I) with bisphosphonates, for use in treatments of proliferative diseases

2. Claims: 2, 11, 17; partly 1, 7-9, 13-15, 20

   Combinations of Epothilone derivatives of formula (I) with platinum compounds, for use in treatments of proliferative diseases.

3. Claims: 12, 18, 19; partly 1, 5-9, 13-15, 20

   Combinations of Epothilone derivatives of formula (I) with vasculostatic compounds, for use in treatments of proliferative diseases and diseases associated with deregulated angiogenesis.

Continuation of Box I.2

Present claims 1, 7-10, 13-16, 20 relate to compositions, methods and uses involving an extremely large number of possible compounds by way of the term "bisphosphonates".
Likewise, present claims 1, 7-10, 13-15, 20 relate to compositions, methods and uses involving an extremely large number of possible compounds by way of the term "platinum compound".
Due thereto, a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search over the complete scope of the claims impossible.

Furthermore, present claims 1, 5, 7-10, 13-15, 18, 20 relate to compositions, methods and uses involving a compound defined by reference to a desirable characteristic or property, namely:
having a vasculostatic effect.
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a limited number of such compounds.
In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). A compound cannot be sufficiently defined by its mechanism of action in vivo and/or its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), supported and disclosed, namely those parts relating to the compounds specifically claimed in the appropriate claim(s) and used in the appropriate example(s).

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 02/08020

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P35/00 A61K31/427 A61K31/282 A61K33/24 A61K31/4439 A61K31/663

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 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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 00485 A (SCHERING AG) 6 January 2000 (2000-01-06)	1,2,5, 7-9,11, 13-18,20
A	page 4-5; claims 1-6,8-10 page 8, line 13-18 page 42-43	12
X	WO 00 49019 A (SCHERING AG) 24 August 2000 (2000-08-24)	1,2,5, 7-9,11, 13-18,20
A	page 2-4; claims 1,5 page 6, line 32-38 page 19, line 21,22 page 24-25	12

-/-

[X] Further documents are listed in the continuation of box C. [X] 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
12 June 2003	23. 06. 2003

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	Kanbier, D

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 18439 A (SCHERING AG) 6 April 2000 (2000-04-06)	1,2,5, 7-9,11, 13-15, 17,18,20
A	page 4-5; claims 1,2,13,15,22 page 9-10	6,12,19
X	WO 99 39694 A (NOVARTIS ERFIND VERWALT GMBH) 12 August 1999 (1999-08-12) cited in the application	1,5,7-9, 13-15, 18,20
Y	page 1, line 21-24; claim 1	1,3,4, 7-10, 13-16,20
A	page 4, line 9-11 page 11, line 20-34 page 12, line 10-31	12
Y	STEARNS M E ET AL: "EFFECTS OF ALENDRONATE AND TAXOL ON PC-3 ML CELL BONE METASTASES INSCID MICE" INVASION METASTASIS, S. KARGER, BASEL, CH, vol. 16, no. 3, 1996, pages 116-131, XP000946388 ISSN: 0251-1789 page 127-129 page 117, right-hand column page 117, right-hand column, paragraph 2 -page 118, left-hand column, paragraph 1	3,7-10, 13-16,20
X	FR 2 775 187 A (NOVARTIS AG) 27 August 1999 (1999-08-27) example 3; table 3	1,5,7-9, 11, 13-15, 17,18,20
Y	page 11, line 22-27; tables 6,8,9 page 12, line 19-35; claims 1,13,16 page 13, line 23-26 page 15, line 19-29 page 20, line 20 -page 21, line 2	3,7-10, 13-16,20
Y	WO 00 59485 A (NOVARTIS ERFIND VERWALT GMBH; NOVARTIS AG) 12 October 2000 (2000-10-12) page 1, paragraphs 2,3; claims 1,5,7 page 2, paragraphs 3,4 page 3, paragraph 3 page 4, paragraphs 3,6 page 23, paragraphs 2,3	1,3,4, 7-10, 13-16,20
Y	WO 00 71104 A (NOVARTIS ERFIND VERWALT GMBH; NOVARTIS AG) 30 November 2000 (2000-11-30) page 2, paragraph 4; claims 1,6 page 7, paragraph 6	1,3,4, 7-10, 13-16,20

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/08020

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 49295 A (UNIV CALIFORNIA) 12 July 2001 (2001-07-12) page 2, line 31,32 page 4-5; claims 1,2,8,25	1,3,4, 7-10, 13-16,20
A	DIEL I J ET AL: "REDUCTION IN NEW METASTASES IN BREAST CANCER WITH ADJUVANT CLODRONATE TREATMENT" NEW ENGLAND JOURNAL OF MEDICINE, THE, MASSACHUSETTS MEDICAL SOCIETY, WALTHAM, MA, US, vol. 339, no. 6, 6 August 1998 (1998-08-06), pages 357-363, XP009005011 ISSN: 0028-4793 page 357-8	1
X	WO 99 01124 A (SLOAN KETTERING INST CANCER) 14 January 1999 (1999-01-14) page 2, line 32-36; claims 1-6,46,47,50	1,5,7-9, 13-15, 18,20
Y	page 33, line 12-17; table 4	1,5,6,8, 9,12-15, 18-20
X	WO 99 02514 A (SQUIBB BRISTOL MYERS CO) 21 January 1999 (1999-01-21) cited in the application page 8, line 20 -page 9, line 17	1,5,7-9, 13-15, 18,20
Y	page 10, line 10-29; claims 1,4,5; examples 3,5-7	1,5,6,8, 9,12-15, 18-20
Y	WOOD J M ET AL: "PTK787/ZK 222584, A NOVEL AND POTENT INHIBITOR OF VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR TYROSINE KINASES, IMPAIRS VASCULAR ENDOTHELIAL GROWTH FACTOR-INDUCED RESPONSES AND TUMOR GROWTH AFTER ORAL ADMINISTRATION" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 60, no. 8, 15 April 2000 (2000-04-15), pages 2178-2189, XP000971163 ISSN: 0008-5472 page 2187; figures 8,9; table 2 page 2183, left-hand column, paragraph 3 -page 2184, left-hand column, paragraph 2	1,5,6,8, 9,12-15, 18-20

-/—

3

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	YANO ET AL: "Treatment for malignant pleural effusion of human lung adenocarcinoma by inhibition of vascular endothelial growth factor receptor tyrosine kinase phosphorylation" CLINICAL CANCER RESEARCH, vol. 6, no. 3, 2000, pages 957-965, XP001151899 page 964	1,5,6,8, 9,12-15, 18-20
P,X	SEIDEN, MICHAEL V.: "Ovarian cancer" ONCOLOGIST (2001), 6(4), 327-332 , XP001159112 page 332, right-hand column	1,5,7-9, 13-15, 18,20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/08020

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0000485	A	06-01-2000	DE	19830060 A1	10-02-2000
			DE	19923001 A1	16-11-2000
			AU	5036999 A	17-01-2000
			WO	0000485 A1	06-01-2000
WO 0049019	A	24-08-2000	DE	19908760 A1	24-08-2000
			AU	3804800 A	04-09-2000
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WO 0018439	A	06-04-2000	DE	19845798 A1	13-04-2000
			AU	1264200 A	17-04-2000
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			AU	2722699 A	23-08-1999
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			BR	9907647 A	14-11-2000
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			AU	2927999 A	15-09-1999
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			CA	2319752 A1	02-09-1999
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			JP	2002504511 T	12-02-2002
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			JP	2002541096 T	03-12-2002
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/08020

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0071104	A		NO	20015638 A	15-01-2002
			NZ	515541 A	28-03-2003
			SK	16682001 A3	04-04-2002
			US	2002142996 A1	03-10-2002
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			AU	5792998 A	25-01-1999
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			US	6204388 B1	20-03-2001
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			US	6300355 B1	09-10-2001
			US	6369234 B1	09-04-2002
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			TR	200000065 T2	21-11-2000
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			ZA	9805938 A	10-01-2000

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

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 4-32073A/078/079

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/EP 02/08020	18 July 2002 (18.07.02)	19 July 2001 (19.07.01)

Title of invention:
COMBINATIONS COMPRISING EPOTHILONES AND PHARMACEUTICAL USES THEREOF

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.)*
CHEN, TianLing
38 Park Street, #18C
Florham Park, NJ 07932
US

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

[X] Further applicants are indicated on a continuation sheet.

Sheet No. .2.

International application No.
PCT/EP 02/08020

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.)*

GREELEY, Diane
46 Lakeview Terrace
Watchung, NJ 07069
US

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

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.)*

ROTHERMEL, John David
46 School House Road
Randolph, NJ 07869
US

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

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.)*

WARTMANN, Markus
Kornfeldstrasse 14
4125 Riehen
CH

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

WOOD, Jeanette Marjorie
In den Kleematten 18
4105 Biel-Benken
CH

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

☐ Further applicants are indicated on another continuation sheet.

Sheet No. 3

International application No.
PCT/EP 02/08020

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

The following person is ☒ agent ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

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

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

Telephone No.
+4161 324 11 11

Facsimile No.
+4161 322 75 32

Teleprinter No.

Agent's registration No. with the Office

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

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

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

☒ the international application as originally filed

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

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

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

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

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

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

Language for the purposes of international preliminary examination: English

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

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

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

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

Box No. V ELECTION OF STATES

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

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

Sheet No. 4.

International application No.
PCT/EP 02/08020

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:			For International Preliminary Examining Authority use only: received	not received
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	☐	☐

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

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☒ other *(specify)*: copy of general authorization 46171

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

19.12.2002

GROS, Florent 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 period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/EP 02/08020	For International Preliminary Examining Authority use only
Applicant's or agent's file reference 4-32073A/078/079	Date stamp of the IPEA

Applicant

Novartis AG et al.

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	EUR 1530.– P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	EUR 159.– H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EUR 1689.– TOTAL	

MODE OF PAYMENT

☒ authorization to charge deposit account with the IPEA (see below)	☐ cash
☐ cheque	☐ revenue stamps
☐ postal money order	☐ coupons
☐ bank draft	☐ other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all IPEAs)

IPEA/ EP

☒ Authorization to charge the total fees indicated above.

☒ *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 2811 0031

Date: 19.12.2002

Name: Novartis AG

Signature: E Rubbhorn H.B

Dr. Friedrich Reimoser
Head of Human Resources
Legal Counsel

Novartis Pharma GmbH
Brunner Str. 59, Postfach 169
A-1235 Vienna/Austria

Tel (++43)-1-86657-493
Fax (++43)-1-86657-760
e-mail: friedrich.reimoser
@pharma.novartis.com

76

NOVARTIS

EPO - Munich
40
15. Nov. 2002

46171

Novartis International AG
Group Intellectual Property
att. Mr. Florent Gros
Postfach
CH-4002 Basel

Oct. 1, 2002

GENERAL AUTHORIZATION

Novartis Pharma GmbH
Brunner Straße 59
A-1230 Wien
Austria

do hereby authorise

Clive Sydney Morris (EPI n°034110)
c/o Novartis AG
Corporate Intellectual Property
Patent and Trademark Department
CH-4002 Basel
Switzerland

to represent us in all proceedings established by the European Patent Convention and to act for us in all patent transactions and to receive payments on our behalf. This authorization shall also apply to the same extent to any proceedings established by the Patent Cooperation Treaty. Additional representatives are indicated on supplementary sheet. Sub-authorization may be given.

Yours faithfully,

Novartis Pharma GmbH
Vienna, October 1, 2002

Signature:

Title: Dr. Erwin Klein, Managing Director; Dr. Friedrich Reimoser, Head of Legal

NOVARTIS

SUPPLEMENTARY SHEET
to GENERAL AUTHORIZATION

Name	EPI No.
Volker Buss	57690
Patrick E. Crawley	50140
Joerg R. Dietz	60600
Florent Gros	87080
Dirk Hillebrand	55300
Timothy Holman	83990
Marc Andreas Markus	99770
Peter de Weerd	92220
Béatrice Molac	49980
Johann Ott	89540
Richard A.M. Ross	35470
Lucien Vallet	41620
Georg von Sprecher	92880
Gérard Wymann	49490
Bernard Marsh	86530
Hans Schaller	84890

Novartis Pharma GmbH,
Vienna, October 1, 2002

Signature:

Title: Dr. Erwin Klein
Managing Director

Dr. Friedrich Reimoser
Head of Legal

PATENT COOPERATION TREATY

PCT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year)	14.11.2003
Applicant's or agent's file reference: 4-32073A/078/079	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/EP02/08020	18.07.2002	19.07.2001

Applicant: NOVARTIS AG

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the International application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

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

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

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

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

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Janzing, M Tel. +31 70 340-4140

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32073A/078/079	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP02/08020	International filing date *(day/month/year)* 18.07.2002	Priority date *(day/month/year)* 19.07.2001
International Patent Classification (IPC) or both national classification and IPC A61K31/00		
Applicant NOVARTIS AG		

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 12 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 sheets.

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

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

Date of submission of the demand	Date of completion of this report
23.12.2002	14.11.2003
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Kanbier, D Telephone No. +31 70 340-3485

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/EP02/08020

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

1-18 as originally filed

Claims, Numbers

1-20 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 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:

INTERNATIONAL PRELIMINARY EXAMINATI N REP RT International application No. PCT/EP02/08020

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. partly 1, 7-10, 13-16, 20

   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. partly 1, 7-10, 13-16, 20 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.

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.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

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	3, 4, 6, 12, 16, 19
	No:	Claims	1, 2, 5, 7-11, 13-15, 17, 18, 20
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	see separate sheet .
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I
Basis of the report

The examination is being carried out on the **following application documents:**
Text for the Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PL PT RO SE SI SK TR
Description, pages:
1-18 as originally filed
Claims, No.:
1-20 as originally filed

The application concerns combinations of epothilones and a bisphosphonate *or* a platinum compound *or* a vasculostatic compound; in the treatments of various forms of cancer.

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

1.
An International Search Report was drawn up for the present set of claims (taking into account considerations of Unity of Invention, see Section IV below), as far as the subject matter included therein is sufficiently defined and supported by (further) claims and by examples, with due regard to the general idea underlying the application as provided by the description.
For subject matter of the present application excluded from the search on this basis, no opinion with regard to novelty and inventive step is included in this preliminary examination.
The following is a specification of the reasons for possible exclusion of part of the application's subject matter from search and thus from preliminary examination:

Present claims 1, 7-10, 13-16, 20 relate to compositions, methods and uses involving an extremely large number of possible compounds by way of the term "bisphosphonates". Likewise, present claims 1, 7-10, 13-15, 20 relate to compositions, methods and uses involving an extremely large number of possible compounds by way of the term "platinum compound".
Due thereto, a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises.
Furthermore, present claims 1, 5, 7-10, 13-15, 18, 20 relate to compositions, methods and uses involving a compound defined by reference to a desirable characteristic or property, namely: having a vasculostatic effect.
The claims cover all compounds having this characteristic or property, whereas

the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a limited number of such compounds.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). A compound cannot be sufficiently defined by its mechanism of action in vivo and/or its pharmacological profile.

Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), supported and disclosed, namely those parts relating to the compounds specifically claimed in the appropriate claim(s) and used in the appropriate example(s), with due regard to the remainder of the description.
Other (non-searched) parts of the application have been excluded from the examination as detailed in Section V below.

2.
Claims 9-12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV
Lack of unity of invention

Rule 13.1 and 13.2 PCT deal with the requirement of unity of invention and state that an international application should relate to only one invention, or to a group of inventions that are linked to form a single general inventive concept. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features". This last expression is defined as meaning a technical feature which defines a contribution which each of the inventions, considered as a whole, makes over the prior art.
In view of the above, the present application lacks unity for the following reasons:

The problem posed in the application is can be formulated as, to provide improved anti-proliferative combinations of active compounds for use in the treatment of proliferative and/or angiogenesis-related disorders.
The solution provided in the application is to use combinations of Epothilone derivatives of claimed formula (I) with bisphosphonates, platinum compounds or vasculostatic compounds in treatments of proliferative diseases or diseases associated with deregulated angiogenesis.

Prior art document WO00/00485 discloses epothilone derivatives according to a

formula which can be combined with e.g. platinum complex compounds or growth factor (e.g. EGF) inhibitors, in the treatment of tumors and as anti-angiogenesis therapy. Presently claimed formula (I) overlaps with formula (I) of WO00/00485.

Furthermore, prior art document WO99/39694 (cited by the applicant in the present application) discloses the use of epothilone A or B, especially epothilone B, in cancer therapy; especially lung or prostate cancer, but also melanoma; where epothilone may be combined with other chemotherapeutic agents, e.g. paclitaxel or doxorubicin (both compounds are "vasculostatic compounds" in the sense of present claim 1, see the present description, page 6).

Thus the idea of using the proposed solution, namely of using combinations of antiproliferative actives comprising the presently claimed epothilone derivatives, to overcome the posed problem is not novel. It therefore cannot serve as a single general inventive concept, linking the various inventions disclosed in the present application.

No further technical feature(s) can be distinguished in the present application that can be regarded as "special technical feature(s)" involved in the technical relationship among the different inventions.
Consequently, the application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different inventions listed below. Each of the inventions is a distinct invention, characterised by its own special technical feature that defines the contribution it makes over the prior art.

Invention 1: claims 3, 4, 10, 16; partly claims 1, 7-9, 13-15, 20
Combinations of Epothilone derivatives of formula (I) with bisphosphonates, for use in treatments of proliferative diseases.

Invention 2: claims 2, 11, 17; partly claims 1, 7-9, 13-15, 20
Combinations of Epothilone derivatives of formula (I) with platinum compounds, for use in treatments of proliferative diseases.

Invention 3: claims 12, 18, 19; partly claims 1, 5-9, 13-15, 20
Combinations of Epothilone derivatives of formula (I) with vasculostatic compounds, for use in treatments of proliferative diseases and diseases associated with deregulated angiogenesis.

For all three inventions listed above, an International Search Report was drawn up and the appropriate further fees were paid in due time. Preliminary examination concerning novelty and inventive step therefore follows in Section V below for each claimed invention.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3. For the assessment of the present claims 9-12 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Reference is made to the following documents:

D1: WO 00 00485 A (SCHERING AG) 6 January 2000

D2: WO 00 49019 A (SCHERING AG) 24 August 2000 (cited in application)

D3: WO 00 18439 A (SCHERING AG) 6 April 2000

D4: WO 99 39694 A (NOVARTIS GMBH) 12 August 1999 (cited in application)

D5: STEARNS M E ET AL: 'EFFECTS OF ALENDRONATE AND TAXOL ON PC-3 ML CELL BONE METASTASES INSCID MICE' INVASION METASTASIS, S. KARGER, BASEL, CH, vol. 16, no. 3, 1996, pages 116-131, XP000946388 ISSN: 0251-1789

D6: FR-A-2 775 187 (NOVARTIS AG) 27 August 1999

D7: WO 00 59485 A (NOVARTIS ERFIND VERWALT GMBH; NOVARTIS AG) 12 October 2000

D8: WO 00 71104 A (NOVARTIS ERFIND VERWALT GMBH; NOVARTIS AG) 30 November 2000

D9: WO 01 49295 A (UNIV CALIFORNIA) 12 July 2001

D10: DIEL I J ET AL: 'REDUCTION IN NEW METASTASES IN BREAST CANCER WITH ADJUVANT CLODRONATE TREATMENT' NEW ENGLAND JOURNAL OF MEDICINE, THE, MASSACHUSETTS MEDICAL SOCIETY, WALTHAM, MA, US, vol. 339, no. 6, 6 August 1998, pages 357-363, XP009005011 ISSN: 0028-4793

D11: WO 99 01124 A (SLOAN KETTERING INST CANCER) 14 January 1999

D12: WO 99 02514 A (SQUIBB BRISTOL MYERS CO) 21 January 1999

D13: WOOD J M ET AL: 'PTK787 / ZK 222584, a novel and potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, impairs vascular endothelial growth factor-induced responses and tumor growth after oral administration' CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 60, no. 8, 15 April 2000, pages 2178-2189, XP000971163 ISSN: 0008-5472

D14: YANO ET AL: 'Treatment for malignant pleural effusion of human lung adenocarcinoma by inhibition of vascular endothelial growth factor receptor tyrosine kinase phosphorylation' CLINICAL CANCER RESEARCH, vol. 6, no. 3, 2000, pages 957-965, XP001151899

INVENTION 1 epothilones + bisphosphonates; exemplified against prostate cancer (zoledronate)

NOVELTY

4. As far as invention 1 is concerned, the application satisfies the requirements of Article 33(1) and (2) PCT in the sense that it claims subject matter that is not anticipated by the prior art (Rule 64 PCT).

INVENTIVE STEP

5. The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject matter of all claims of invention 2 does not involve an inventive step (Rule 65(1)(2) PCT) in view of D5 and D6, and in view of D4 and D8.

(i) D5 (considered to be the closest prior art for this invention) discloses effective combinations of alendronate and taxol in a prostatic cancer murine model. Page 117 mentions that results are not generalisable to all bisphosphonates since some of them give contrary results. There is no reference to replacing taxol with epothilones (page 117, right column - page 118, left column, paragraph 1). However, D6 discloses the application of epothilones, especially Epo B, to treatments of melanoma, lung cancer, prostate cancer (page 12) and also angiogenesis (page 13). Combinations are envisaged with a list of classes of actives, including taxol and doxorubicin (page 20). Example 3 and table 3 show that Epo B is more beneficial than taxol when applied in treatments of prostate cancer.
Difference between D5 and the present application is the use of taxol in the combination against prostate cancer. Faced with the problem of providing alternative combinations comprising alendronate against prostate cancer, and knowing about D6 (especially example 3, page 56, lines 25-26 and table 3), a skilled person would, without inventive effort, replace taxol with Epo B, thus leading to the subject matter of present claims 1, 3, 7-10, 13-16 and 20.

(ii) Both epothilones (D6, D4) and bisphosphonates (D5, D7, D8, D9) are known for their effectiveness in treating prostate cancer (and as anti-cancer agents in general; see D1, D2 resp. D10). It does not require an inventive step for a skilled person to combine two anti-prostate cancer agents in a combined amount effective to treat prostate cancer, unless an unexpected technical effect is revealed in doing so (e.g. synergy). Such a combination would be expected by a skilled person to show at least some beneficial effect, such as an additive effect (the same applies to any other envisaged form of cancer as presently claimed). In this sense, all claims 1, 3, 4, 7-10, 13-16 and 20 lack an inventive step in view of the prior art.

The selection of zoledronic acid (present claim 4), a well-known bisphosphonate, does not seem to bring about any further technical effect that would justify the

acknowledgment of an inventive step in view of remark V.5.(ii) above. However, in view of D5, page 117, demonstration of the effectiveness of zoledronic acid in combination with an epothilone (for example in the form of the results of the experiment described in present example 2), would be enough to acknowledge inventive step of this particular embodiment.

INVENTION 2 Epothilones + platinum compounds; exemplified against lung cancer (carboplatin) and prostate cancer (oxaliplatin)

NOVELTY

6. The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of Claims 1, 2, 7-11, 13-15, 17 and 20 lacks novelty in respect of prior art documents D1, D2 and D3 as defined in the regulations (Rule 64(1)-(3) PCT).

6.1 D1 discloses epothilones of overlapping formula with the epothilones presently claimed (including Epo B; pages 4-5 and page 8, lines 13-18), which can be combined with, amongst others, platinum complexes such as cisplatin and carboplatin (page 42, lines 20-21) in the treatment of, amongst others, melanoma and lung-, colon-, ovarian- and head- and neck cancers (page 42, lines 8-10). Thus D1 anticipates the subject matter of present claims 1, 2, 7-11, 13-15, 17 and 20.

6.2 D2 discloses epothilones of overlapping formula with the epothilones presently claimed (including Epo B) when considering that for the purposes of the present invention as claimed (anti-cancer activity of the epothilones), the presence of H isotopes deuterium or tritium instead of "normal" H atoms does not make any difference. The epothilones can be combined with, amongst others, platinum complexes such as cisplatin or carboplatin (page 24, lines 22-23) in the treatment of, amongst others, melanoma and lung-, colon-, ovarian- and head- and neck cancers (page 24, lines 9-10). Thus D2 anticipates the subject matter of present claims 1, 2, 7-11, 13-15, 17 and 20.

6.3 D3 discloses conjugates for use in anti-cancer therapy comprising an epothilone and a platinum complex (preferably cisplatin) or a vasculostatic compound on a carrier molecule (claims 22, 2, 12, 13 and 15; page 4). No specific types of cancer are mentioned. Thus D3 anticipates the subject matter of present claims 1, 2, 7-10, 13-15, 17 and 20.

INVENTIVE STEP

7. Even if formal novelty of the above Claims can be reinstated, the present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of Claims 1, 2, 7-11, 13-15, 17 and 20 does not involve an inventive step (Rule 65(1)(2) PCT) in view of D6 or D4 and D1-D3.

7.1 D6 and D4 disclose the use of Epothilones A and B, especially Epo B (D6: claim 1, pages 1,22; D4: page 1 and page 4, paragraph 3), as anti-cancer agents against e.g. lung- and prostate cancers (D6: example 3, Table 3, Table 6, Table 8,

page 12, lines 19-35, claims 13, 16; D4: page 11, paragraph 4). Epo B (or Epo A) can be combined with other active agents such as alkylating agents (D6: page 20, lines 20-25; D4:).

7.2 It is part of common knowledge that the class of alkylating anti-cancer agents includes platinum complexes such as cisplatin, carboplatin and oxaliplatin, which are well-known and very commonly used anti-cancer agents, and which are also indicated in combinations with epothilones in D1, D2 and D3.

7.3 Thus, from D6 or D4, the problem confronting the skilled person of providing combinations of agents for treating e.g. lung- or prostate cancer, as indicated in D6 and D4, would be solved with no inventive effort by using platinum complexes such as cisplatin, carboplatin or oxaliplatin as alkylating agents, thus arriving at the subject matter of present claims 1, 2, 7-11, 13-15, 17 and 20.

D1, D2 and D3 do not mention oxaliplatin. If, for the use of oxaliplatin a beneficial activity in the present combinations is demonstrated, *and* a technical effect obtained by choosing a particular platinum complex and a particular epothilone from present formula (I) is also demonstrated, inventive step of such specific combinations could probably be acknowledged.

INVENTION 3 Epothilones + vasculostatic compounds, exemplified against prostate cancer and melanoma (PTK 787)

NOVELTY

8. The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of Claims 1, 5, 7-10, 13-15, 18 and 20 lacks novelty in respect of prior art documents D4, D6, D11 and D1-D3 as defined in the regulations (Rule 64(1)-(3) PCT).

8.1 D4 and D6 disclose anti-cancer combinations of epothilones A and B (especially B, pages 1,4 resp. pages 1,11, claim 1) with e.g. doxorubicin and (especially) taxol (page 12, lines 18-31 resp. page 20, lines 26-27); treatment of e.g. prostate cancer and melanoma, and deregulated angiogenesis (D6, page 13) is envisaged (page 11, lines 21-22 resp. page12). Doxorubicin and taxol are examples of vasculostatic agents according to the present application (pages 5,6). Thus D4 and D6 anticipate the subject matter of present claims 1, 5, 7-10, 13-15, 18, 20.

8.2 In Table 4, D11 discloses combinations of Epo B and taxol that have a combination index of >1, indicating synergy, in treatments of leukemia (cell-line CCRF-CEM). D11 combines epothilone derivatives, including Epo A and B (claims 3, 4 with R being H, CH3) with cytotoxic anticancer agents, e.g. paclitaxel (claims 45-47, 50). Treatment of melanoma is envisaged (page 33, lines 12-17). Thus D11 anticipates the subject matter of present claims 1, 5, 7-10, 13-15 and 20.

8.3 D1 and D2 disclose combinations not only with platinum complexes as described above, but also with doxorubicin, taxanes such as taxol and taxotere, growth factor inhibitors such as EGF inhibitors, e.g. suramin; and PTK inhibitors (page 42, lines 22-35 resp. page 24, lines 24-34); treatments of melanoma, prostate cancer

and deregulated angiogenesis are envisaged (page 42 resp. page 24). Compounds of the latter list have been disclosed in the present application as possible vasculostatic compounds (pages 5-6). Thus D1 and D2 anticipate the subject-matter of present claims 1, 5, 7-10, 13-15, 18 and 20.

8.4 Likewise, D3 not only discloses combined compounds with cisplatin, the preferred agent, but also with e.g. doxorubicin, suramin, taxol and PTK blockers (pages 4-5) and growth factor inhibitors such as angiostatin and endostatin (pages 9-10). These compounds also fall in the list of presently disclosed vasculostatic compounds (pages 5-6). Thus D3 anticipates the subject matter of present claims 1, 5, 7-10, 13-15 and 20.

INVENTIVE STEP

9. Even if formal novelty of the above Claims can be reinstated, e.g. by an appropriate amendment, the present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of Claims 1, 5, 7-10, 13-15, 18, 20 and 6, 12 and 19 does not involve an inventive step (Rule 65(1)(2) PCT) in view of D1/D2 and D13/D14.

9.1 Combining an epothilone with a VEGF inhibitor (D1, D2) or PTK inhibitor (D3) as a growth factor inhibitor of choice, in treatments of various forms of cancer, is known from D1, D2 and D3. To replace the indicated VEGF or PTK inhibitor in D1, D2 and D3 with PTK 787 would not require inventive effort in view of D13 and D14 (disclosures detailed below), since both documents indicate that PTK 787 presents various advantages over other, known VEGF / PTK inhibitors.

9.3 D13 discloses application of PTK 787 on solid tumors and other diseases where angiogenesis plays a role, e.g. on the DU145 prostate carcinoma cell line, and cell lines for vaginal (A431) and colon carcinoma (page 2183 and figure 8). Combinations with conventional antitumor therapies are envisaged (page 2187, right column, paragraph 1). PTK 787 is stated to bring advantages over known VEGF / PTK inhibitors (page 2187, right column, paragraph 2).
D14 discloses the effective use of PTK 787 in the treatment of lung cancer-associated malignant PE. The effect of PTK 787 is that vascularization and total volume of the tumor is inhibited. It is envisaged that PTK 787 is used in treating lung cancer patients receiving long-term treatment (i.e., combinations with other anti-cancer agents). PTK 787 is stated to demonstrate various advantages over other known VEGF inhibitors (page 964, left column, paragraph 3).
In both D13 and D14, PTK 787 is also stated to be a VEGF PTK inhibitor.

24.08.2003
4 -32073A/078/079
James Stuttle

VT
PCT
EP02/08020

Corporate Intellectual Property
27. Juni 2003
APPL. | M/D | F/L | PS | Copy:

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

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

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	24/06/2003
Applicant's or agent's file reference: 4-32073A/078/079	REPLY DUE: within 2/ 00 months/days from the above date of mailing
International application No.: PCT/EP 02/ 08020	International filing date *(day/month/year)*: 18/07/2002
Priority date *(day/month/year)*: 19/07/2001	
International Patent Classification (IPC) or both national classification and IPC: A61K31/00	
Applicant: NOVARTIS AG	

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 [X] Basis of the opinion
- II [ ] Priority
- III [X] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV [X] Lack of unity of invention
- V [X] 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 66.4*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: 19/11/2003

Name and mailing address of the IPEA/
European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer
Examiner

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

Form PCT/IPEA/408 (cover sheet) (march 2002)

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).

IV. Lack of unity of invention

The objection as to lack of unity raised in the international search report is maintained. The reasons for the objection are the same as those indicated in the 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.

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION 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 presenta	( )	( )
- la solicitud.		
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

Fecha:

SUPERINDUSTRIA Y COMERCIO SISTEMA DE REGISTRO

Fecha 05/03/2004

MANTENIMIENTO DE PROTOCOLOS

Numero : 17398
Fecha : 16/04/1997
Conferido: NOVARTIS AG (NOVARTIS SA) (NOVARTIS INC.)
Pais : CH SUIZA
Ciudad : 3 BASILEA
Represent: S Sustituir : S Desistir : S
No. Radicacion : 97 19953 Clase: 0 Seev: 0 Seac: 0

Secncia	Codigo Ctr	Nombre
1	5376	ESCOBAR URIBE JIMENA
2	267	ESCOBAR URIBE IGNACIO

Encontrados (1/1) registro(s)

Industria y Comercio
SUPERINTENDENCIA

95 95

2020
Bogotá, D.C.,

Doctora:
Jimena Escobar Uribe
Apoderada
Novartis AG.

Oficio N° 03247

ASUNTO:	Radicación N°	04-11525
	Solicitud internacional	PCT/EP02/08020
	Fecha Inicio fase nacional	19/02/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento el 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 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 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 26 MAR. 2004.

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