

Industria y Comercio
SUPERINTENDENCIA

33 011645 00

SUPERINTENDENCIA Y COMERCIO
Radicación 03011545 00000000 Folios 06
Fecha (AMB) 2003-02 12 17 06 37
Trámite 011 PCT-PATENT 370 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE

PCT

19358

ENTRADA EN FASE NACIONAL

1 SOLICITUD DE			
☒ Patente de Invención		☐ Patente de Modelo de Utilidad	
☒ Capítulo I		☒ Capítulo II	
2 SOLICITANTE (71)	Nombre BRISTOL - MYERS SQUIBB COMPANY Dirección P O Box 4000 Princeton NJ 08543-4000 Estados Unidos de América Nacionalidad o Domicilio Estados Unidos Lugar de Constitución Estados Unidos Teléfono: Fax: E-mail:		IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre RAMIRO CASTRO DUQUE Dirección Cra 7 No 16-56 Piso 9 Teléfono 380-2200 Fax. 380-2700 E-mail:		IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 170.322 TP 1003
4 INVENTOR (ES) (72)	Nombre John D Dimarco/Jack Z Gougoutas/Imre M Vitez/Martha Davidovich/Michael Galella/Timothy M Malloy/Zhenrong Guo/Denis Favreau/ Dirección 16 Neal Drive East Brunswick NJ 08816, US 101 Westarly Road Princeton NJ 08540 US 117 Main Street, Whitehouse Station NJ 08889 US 159 Fern Road East Brunswick, NJ 08816 US 3 Evergreen Court, Belle Mead, NJ 08502 US, 1902 Makefield Road, Yardley PA 19067 US 21 Augusta Place East Brunswick, NJ 08816 US 5065 Terrasse Beaudry Saint-Hubert, Quebec J3Y 6L2 CA Respectivamente Nacionalidad o Domicilio Estados Unidos de América y Canadá Respectivamente		
5 PCT (88) Solicitud Internacional No PCT/US01/24540 Fecha 01-08-2001 Publicación Internacional No WO 02/14323 A2 Fecha 21-02-2002			
Título (54): POLIMORFOS DE UN ANALOGO DE EPOTILONA			
7 Clasificación Internacional (51) C07D491/00 // A61K31/7048			
8 Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☒ NO ☐	US	16-08-2000	60/225.590
Comprobante de pago No 103-25-201 Fecha 21/02/2003			

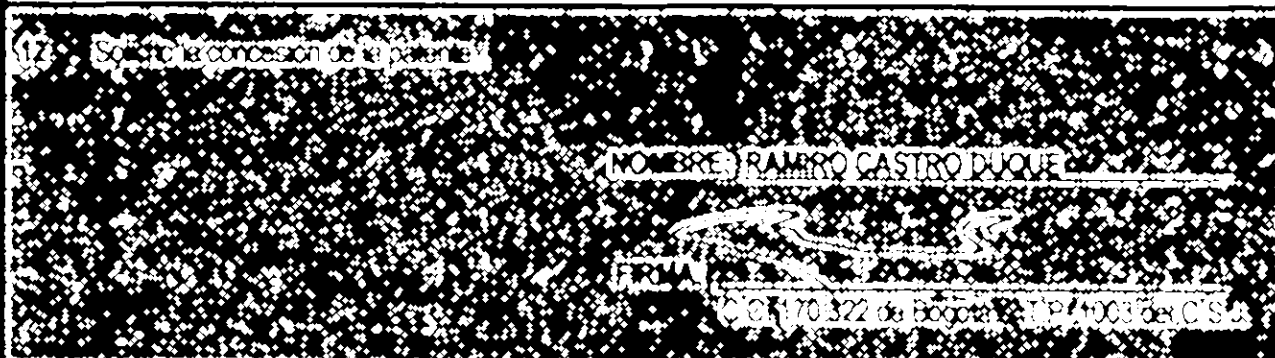
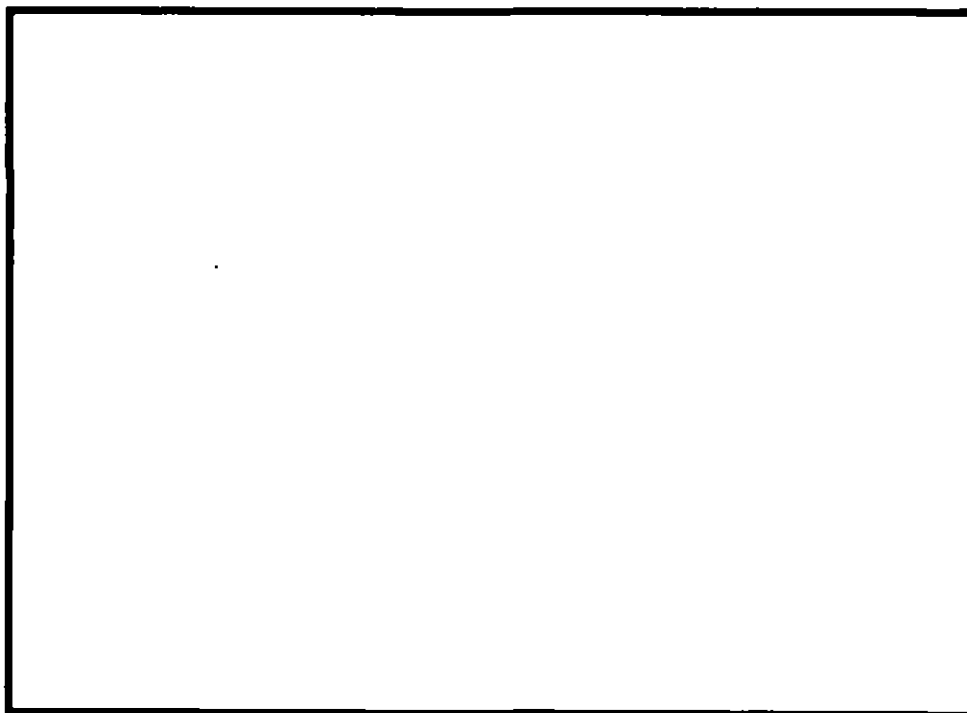
10

ANEXOS

002

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$400.000
- ☒ Comprobante de pago por reivindicación de prioridad. \$112.000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Protocolo No. 19358
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

11 FIGURA CARACTERÍSTICA:



Instrucciones para la presentación de los anexos, ver reverso de esta página.

NIT : 900176009-2



Industria y Comercio
SUPERINTENDENCIA

RECIBO OFICIAL DE CAJA : 03 - 255
FECHA : ENERO 2 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PAGO	Vr. PAGO
BRISARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	7416981	02/01/2003	9,728,000.00

***** CONCEPTO *****

CANT. CONTABILITICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	82 INVOCACION DE UNA PRIORIDAD EN MU	112,000.00
	TOTAL :	\$ 112,000.00

SON: CIENTO DOCE MIL PESOS

RESPONSABLE :

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radicacion : 03011545 00000000 Folios: 06
Fecha (AMB): 2003-02-12 17:06:37
Tramite : 011 PCT-PATENT 378 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO DE CAJA APLICADO AL EXPEDIENTE Nº. _____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

NIT : 800176089-2



Industria y Comercio
SUPERINTENDENCIA

RECIBO OFICIAL DE CAJA : 03 - 261
FECHA : ENERO 2 DE 2003

**** CONSIGNACION ****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRISARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	7416981	02/01/2003	9,720,000.00

**** CONCEPTO ****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
	TOTAL :	\$ 400,000.00

SOM: CUATROCIENTOS MIL PESOS

RESPONSABLE :

SUPERINTENDENCIA Y COMERCIO
Radicacion : 83011545 00000000 Folios: 86
Fecha (AMD): 2003-02-12 17:06:37
Tramite : 011 PCT-PATENT 370 FASE INCI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

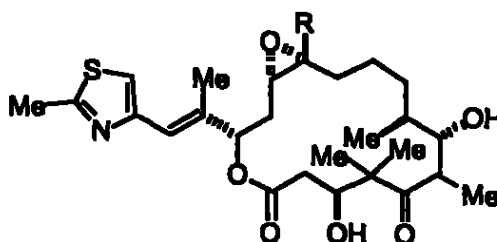
POLIMORFOS DE UN ANÁLOGO DE EPOTILONA

Campo de la Invención

La presente invención se relaciona con formas polimórficas cristalinas de un análogo de epotilona altamente potente que está caracterizado por mejoradas propiedades.

Antecedentes de la Invención

Las epotilonas son compuestos macrólidos que encuentran utilidad en el campo farmacéutico. Por ejemplo, Epotilonas A y B que tienen las estructuras:



Epotilona A R = H

Epotilona B R = Me

pueden encontrarse para ejercer efectos estabilizantes de micro tubulos similares al paclitaxel (TAXOL[®]) y consecuentemente actividad citotóxica contra células que proliferan rápidamente, tales como, células de tumores u otra enfermedad celular hiper-proliferativa, ver Hofle, G., y otros, Angew. Chem. Int. Ed. Engl., Volumen 35, No. 13/14, 1567-1569 (1996);

W093/10121 publicada en Mayo 27, 1993; y W097/19086 publicada en Mayo 29, 1997.

Varios análogos de epotilona han sido sintetizados y pueden usarse para tratar una variedad de cánceres y otras enfermedades proliferativas anormales. Dichos análogos se divulgan en Hofle y otros, Id.; Nicolaou, K.C., y otros, Angew Chem. Int. Ed. Engl., Volumen 36, No. 19, 2097-2103 (1997); y Su, D.S., y otros, Angew Chem. Int. Ed. Engl., Volumen 36, No. 19, 2093-2097 (1997).

Un análogo de epotilona particularmente ventajoso que se ha encontrado que tiene ventajosa actividad es [1S- [1R*,3R*(E),7R*,10S*,11R*,12R*,16S*11-7,11-Dihidroxi-8,8,10,12,16-pentametil-3-[1-metil-2-(2-metil-4-tiazolil)etenil]-4-aza-17-oxabicyclo[14,1.0]heptadecano-5,9-diona. De acuerdo con la presente invención, dos formas de cristales del sujeto análogo de epotilona se proporcionan. Estos polimorfos, los cuales se han designado como Formas A y B, respectivamente, son formas novedosas de cristales y se identifican aquí abajo.

Breve Descripción de los Dibujos

La Figura 1 es un patrón de difracción de rayos x en polvo (CuK α λ =1,5406 Å a temperatura ambiente) de Forma A del sujeto análogo de epotilona.

La Figura 2 es un patrón de difracción de rayos x en polvo de Forma B (CuK α λ =1,5406 Å a temperatura ambiente) del sujeto análogo de epotilona.

La Figura 3 es un patrón de difracción de rayos x en polvo de una mezcla de Formas A y B ($\text{CuK}\alpha$ $\lambda=1,5406$ Å a temperatura ambiente) del sujeto análogo de epotilona.

La Figura 4 es una comparación de los patrones de difracción de rayos x en polvo simulado y actual de las Formas A y B del sujeto análogo de epotilona.

La Figura 5 es un espectro Raman de la Forma A del sujeto análogo de epotilona.

La Figura 6 es un espectro Raman de la Forma B del sujeto análogo de epotilona.

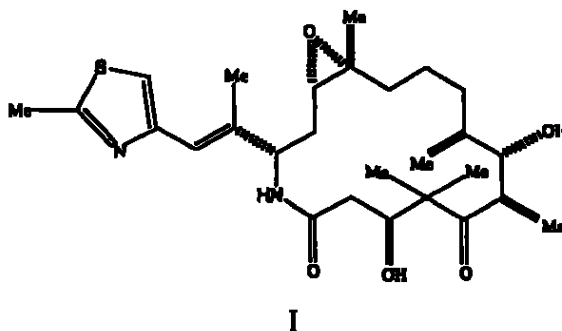
La Figura 7 es un espectro Raman de una mezcla de las Formas A y B del sujeto análogo de epotilona.

La Figura 8 ilustra la conformación de estado sólido en la Forma A del sujeto análogo de epotilona.

La Figura 9 ilustra la conformación de estado sólido en la Forma B del sujeto análogo de epotilona.

Resumen de la Invención

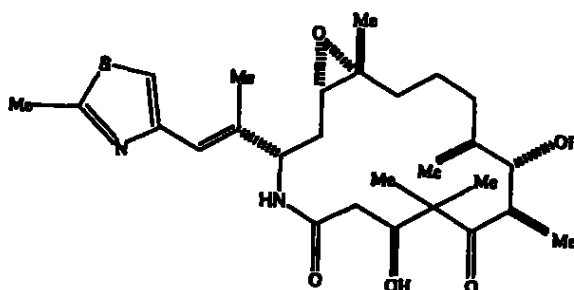
De acuerdo con la presente invención, se proporcionan dos polimorfos cristalinos del análogo de epotilona representado por la fórmula 1.



Uno de estos polimorfos, designado Forma A, se ha encontrado que tiene propiedades particularmente ventajosas. La presente invención está dirigida hacia Forma A y Forma B cristalinas de polimorfos así como sus mezclas. La presente invención pertenece adicionalmente al uso de estas formas cristalinas en el tratamiento de cánceres y otras enfermedades proliferativas y formulaciones farmacéuticas que las contienen.

Descripción Detallada de la Invención

De acuerdo con la presente invención, se proporcionan polimorfos de un análogo de epotilona representado por la fórmula 1 de abajo



I

El análogo de epotilona representado por la fórmula I es químicamente [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihidroxi-8,8,10,12,16-pentametil-3-[1-metil-2-(2-metil-4-tiazolil)etenil]-4-aza-17-oxabicyclo[14.1.0]heptadecano-5,9-diona. Este análogo y su preparación se describe en la solicitud de patente U.S. Serie No. 09/170,582, presentada en Octubre 13, 1998, cuya divulgación se incorpora aquí a modo de referencia. Los polimorfos del análogo representado por la fórmula I de arriba son agentes de estabilización de micro tubulos. Ellos son consecuentemente útiles en el tratamiento de una

variedad de cánceres y otras enfermedades proliferativas que incluye, pero no está limitada a, las siguientes;

- carcinoma, incluyendo el de la vejiga, seno, colon, riñón, hígado, pulmón, ovario, páncreas, estómago, cerviz, tiroides y piel, incluyendo carcinoma de célula escamosa;
- tumores hematopoiéticos de linaje linfoide, incluyendo leucemia, leucemia linfocítica aguda, leucemia linfoblástica aguda, linfoma de células B, linfoma de células T, linfoma de Hodgkins, linfoma no de Hodgkins, linfoma de células del pelo y linfoma de Burketts;
- tumores hematopoiéticos de linaje mieloide, incluyendo leucemias mielógenas aguda y crónica y leucemia promielocítica;
- tumores de origen mesen químico, incluyendo fibra-sarcoma y rabdo mios-carcoma;
- otros tumores, incluyendo melanoma, seminoma, teratocarcinoma, neuroblastoma y glioma;
- tumores del sistema nervioso central y periférico, incluyendo astrocitoma, neuroblastoma, glioma, y schwannomas;
- tumores de origen mesen químico, incluyendo fibra-sarcoma, rabdo mios-carcoma, y osteo-sarcoma; y otros tumores, incluyendo melanoma, xerodermia pigmento zum, keratoacantoma, seminoma, cáncer folicular de tiroides y teratocarcinoma.

Los polimorfos sujeto inhibirán además la angiogenesis, afectando así el crecimiento de tumores y proporcionando tratamiento de tumores y desórdenes relacionados con tumores. Dichas propiedades de anti-angiogenesis serán útiles además en el tratamiento de otras condiciones responsables de los agentes anti-angiogenesis incluyendo, pero no limitados a, algunas formas de ceguera relacionada con vascularización de

la retina, artritis, especialmente artritis inflamatoria, esclerosis múltiple, restenosis y soriasis.

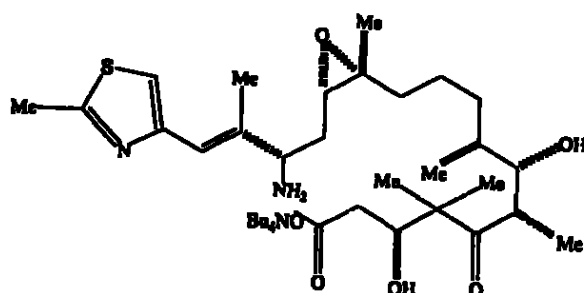
Los polimorfos del análogo representado por la fórmula I inducirán o inhibirán la apoptosis, un proceso de muerte de células fisiológico crítico para el normal desarrollo y homeostasis. Las alteraciones de vías apoptóticas contribuyen a la patogénesis de una variedad de enfermedades humanas. Los polimorfos sujeto, como moduladores de apoptosis, serán útiles en el tratamiento de una variedad de enfermedades humanas con aberraciones en apoptosis incluyendo, pero no limitadas a, cáncer y lesiones pre-cancerosas, enfermedades relacionadas con respuesta inmune, infecciones virales, enfermedades degenerativas del sistema músculo-esquelético y enfermedad del riñón.

Sin desear estar ligados a cualquier mecanismo o morfología, las tales formas cristalinas del análogo de epotilona representado por la fórmula I pueden usarse además para tratar condiciones diferentes al cáncer u otras enfermedades proliferativas. Dichas condiciones incluyen, pero no están limitadas a infecciones virales tales como virus de herpes, virus de pox, virus de Epstein-Barr, virus de Sindbis y virus adeno; enfermedades auto-inmunes tales como lupus sistémico eritematoso, glomérulo nefritis mediada inmune, artritis reumatoide, soriasis, enfermedades inflamatorias del baso y diabetes mellitus auto inmune; desordenes neuro-degenerativos tales como enfermedad de Alzheimer, demencia relacionada con SIDA, enfermedad de Parkinson, esclerosis lateral amiotrófica, retinitis de pigmentos, atrofia muscular espinal y degeneración del cerebelo; SIDA; síndromes mielo displásticos; anemia aplástica; daño isquémico asociado con infartos del miocardio; ataque y daño de reperfusión; restenosis; arritmia; aterosclerosis; enfermedades del

hígado inducidas por toxinas o alcohol; enfermedades hematológicas tales como anemia crónica y anemia y aplástica; enfermedades degenerativas del sistema músculo-esquelético tal como osteoporosis y artritis; rinosinusitis sensible a aspirina; fibrosis cística; esclerosis múltiple; enfermedades del riñón; y dolor del cáncer.

La cantidad efectiva de los polimorfos sujeto, particularmente Formas A, pueden determinarse por una persona experta en el arte, e incluye cantidades de dosificación de ejemplo para un humano de desde alrededor de 0,05 a 200 mg/kg/día, que puede administrarse en una sola dosis o en forma de dosis individuales divididas, tal como desde 1 a 4 veces por día. Preferiblemente los polimorfos sujeto se administran en una dosificación de menos de 100 mg/kg/día, en una sola dosis o en 2 a 4 dosis divididas. Se entenderá que el nivel de dosis específica y la frecuencia de dosificación para un sujeto particular puede variar y dependerá de una variedad de factores incluyendo la actividad del compuesto específico empleado, la estabilidad metabólica y la longitud de acción de ese compuesto, la especie, edad, peso corporal, salud general, sexo y dieta del sujeto, el modo y tiempo de administración, velocidad de excreción, combinación de drogas, y severidad de la condición particular. Los polimorfos sujeto se administran preferiblemente en forma parenteral, sin embargo, otras rutas de administración están aquí contempladas como son reconocidas por aquellos expertos en las artes de la oncología. Preferidos sujetos para tratamiento incluyen animales, más preferiblemente especies mamíferas tales como humanos, y animales domésticos tales como perros, gatos y similares, sujetos a los anteriormente mencionados desórdenes.

La preparación de los análogos de epotilona representados por la fórmula I descritos en la solicitud de patente U.S. Serie No. 09/170,582 produjo el análogo de epotilona sujeto como un aceite que puede cromatografiarse y purificarse para lograr un polvo amorfo. Una preparación preferida se describe en una solicitud de continuación bajo la Serie No. 09/528,526 presentada en Marzo 20, 2000, cuya divulgación se incorpora aquí a modo de referencia. En esta preparación, tal como pertenece a los análogos representados por la fórmula I, la epotilona B reacciona con un agente donante de ázido, y un agente de amortiguación en presencia de un catalizador de paladio y un agente de reducción para formar un intermediario representado por la fórmula



Una reacción de macro-lactamización se lleva entonces a cabo sobre el intermediario para formar el análogo representado por la fórmula I. Se ha encontrado ahora que este análogo, en su forma cristalina, consiste de una mezcla de Formas A y B como se describe completamente aquí. La forma amorfa del análogo de epotilona representada por la fórmula I puede desarrollarse en un solvente adecuado, preferiblemente un solvente mezclado tal como acetato de etilo/diclorometano/trietilamina, purificado tal como mediante filtración de almohadilla sobre gel de sílice, y cristalizado enfriando a una temperatura de alrededor de 5°C para formar un material cristalino que es una mezcla de Forma A y Forma B. El paso

de purificación que usa una mezcla de solventes que contiene un componente tal como diclorometano retira los solventes residuales de la síntesis que puede interferir con el proceso de cristalización.

Generalmente, tomando el material purificado en una cantidad limitada de acetato de etilo y calentando el precipitado resultante a alrededor de 75 a 80°C causará la formación de Forma A. Cantidad limitada significa desde alrededor de 8 a 16 mL, preferiblemente desde alrededor de 8 a 12 mL, de acetato de etilo por gramo de material purificado. A medida que la solución es calentada, se forma un precipitado delgado el cual se ha encontrado que es predominantemente Forma B. A alrededor de 75°C el precipitado sufre un adelgazamiento de material el cual se ha encontrado ser la formación de Forma A. El precipitado es mantenido a alrededor de 75 a 80°C durante alrededor de una hora para asegurar la terminación de la formación de Forma A en cuyo tiempo se agrega ciclohexano al precipitado en una relación de acetato de etilo de de desde alrededor de 1:2 a 2:2, preferiblemente alrededor de 1:2, y la mezcla se deja enfriar a temperatura ambiente a la cual se mantiene con agitación durante un periodo de desde alrededor de 12 a 96 horas. La mezcla se enfría entonces a alrededor de 5°C durante alrededor de dos horas después de lo cual los cristales de Forma A del análogo de epotilona sujeto se recuperaron. La Forma A se logra en buen obtenido y pureza.

Procedimientos alternativos para la preparación de Forma A involucran la adición de cristales de semillas. En las descripciones que siguen se usaron los cristales de semillas de Forma A, pero los cristales de semilla de Forma B, o sus mezclas pueden usarse igualmente. En un procedimiento tal, el material purificado se desarrolla en una cantidad limitada de acetato de etilo como se describe arriba y se calienta a

alrededor de 75°C, se agregan cristales de semilla y la mezcla se mantiene durante alrededor de 30 minutos. Una cantidad de ciclohexano como se describe arriba se agrega entonces gota a gota manteniendo la temperatura a alrededor de 70°C. La mezcla se enfría posteriormente a 20°C y se mantiene con agitación durante 18 horas después de lo cual se enfría a 5°C y los cristales blancos de Forma A se recuperan por separación física, por ejemplo, filtración.

En un segundo procedimiento, la solución de material inicial en acetato de etilo se calienta a 75°C durante por lo menos una hora hasta que se produce una solución. La solución se enfría a alrededor de 50°C durante el curso de alrededor de dos horas agregando cristales de semilla de Forma A cuando la temperatura alcanza alrededor de 60°C. Los cristales comienzan a aparecer a alrededor de 55°C. La temperatura se reduce nuevamente a alrededor de 20°C durante adicionales dos horas durante cuya una hora una cantidad de ciclohexano como se describe arriba se agrega gota a gota. El precipitado final se enfría adicionalmente durante dos horas y se mantiene a -10°C y se mantiene a esa temperatura durante una hora adicional. El precipitado se filtra entonces para lograr cristales blancos de Forma A.

En un adicional procedimiento alternativo, el material se desarrolla en una mayor cantidad, es decir de por lo menos alrededor de 40 mL/g de acetato de etilo y el precipitado resultante se calienta a alrededor de 80°C hasta que se forma una solución la cual se enfría entonces a alrededor de 70°C durante el curso de alrededor de una hora. Los cristales de semilla de Forma A se agregan cuando la temperatura de la solución alcanza alrededor de 70°C. La temperatura se reduce entonces a alrededor de 30°C durante adicionales tres horas. Los cristales comienzan a aparecer a

alrededor de 65°C. La temperatura se reduce a -10°C durante adicionales tres horas durante cuyo periodo de treinta minutos una cantidad de ciclohexano como se describe arriba se agrega gota a gota. La temperatura se mantiene a -10°C durante una hora adicional. El precipitado final se filtra para lograr cristales blancos de Forma A. El obtenido y la pureza de la Forma A mediante estos procedimientos se consideran muy buenos.

La Forma B de los análogos de epotilona sujeto representada por la fórmula I de arriba se obtiene formando un precipitado del material crudo en una mayor cantidad de acetato de etilo, es decir desde alrededor de 40 a 50 mL por gramo, y calentando a 70°C hasta 80°C durante una hora para formar una solución la cual es entonces mantenida a una temperatura durante alrededor de treinta minutos. La solución se enfría a alrededor de 30°C durante el curso de alrededor de dos horas, los cristales comienzan a aparecer a alrededor de 38°C. La temperatura se reduce adicionalmente a alrededor de -10°C durante una hora durante lo cual una cantidad de ciclohexano como se describe arriba se agrega gota a gota durante un periodo de treinta minutos. El precipitado final se mantiene a -10°C durante adicionales dos horas y se filtra para lograr cristales blancos de Forma B.

En una preparación alternativa a la de arriba, el material crudo se precipita con una cantidad similar de acetato de etilo y se calienta a alrededor de 78°C para formar una solución que se mantiene entonces a esa temperatura durante alrededor de treinta minutos. La solución se enfría a alrededor de 10°C durante el curso de alrededor de dos horas y los cristales de semilla de Forma A se agregan cuando la temperatura alcanza alrededor de 10°C. La temperatura se reduce nuevamente durante adicionales dos horas a -10°C durante un periodo de treinta minutos

durante el cual una cantidad de ciclohexano como se describe arriba se agrega gota a gota. La temperatura se mantiene a -10°C durante dos horas. El precipitado final se filtra para lograr cristales blancos de Forma B.

En un adicional procedimiento alternativo, el material purificado se desarrolla en otro solvente, preferiblemente tolueno, en una cantidad entre alrededor de 10 y 20 mL por gramo, y se calienta a 75°C hasta 80°C durante 30 minutos y luego se enfría a 20°C y se mantiene durante 18 horas con agitación. Los cristales blancos de Forma B se recuperan del precipitado mediante separación física. El obtenido y pureza de Forma B mediante estos procedimientos se consideran muy buenos.

Las Figuras 1 a 3 son patrones de difracción de rayos x en polvo de Formas A, B y una mezcla de ellos, respectivamente, del análogo sujeto. La Figura 4 es una comparación de los patrones de difracción de rayos x en polvo simulados a partir de estructuras de un solo cristal para las Formas A y B con el patrón actual para cada una. Los patrones de difracción de rayos x se generaron a partir de un Philips Xpert con una fuente generadora de 44kV y 40 mA y un filamento $\text{CuK}\alpha$ de $k = 1,5406 \text{ \AA}$ a temperatura ambiente. En los resultados mostrados en las Figuras 1 a 4, así como en las Tablas 1 y 2 de abajo que contienen los datos en forma resumida, las diferencias establecen claramente que las Formas A y B del análogo de epotilona sujeto posee diferentes estructuras cristalinas. En las Tablas, las Intensidades Pico de desde 1 a 12 se clasifican como muy débiles, desde 13 a 32 como débiles, desde 33 a 64 como promedio, desde 65 a 87 como fuertes y desde 88 a 100 como muy fuertes.

Tabla 1
Valores para Forma A

Posición Pico (dos teta) (CuK α λ = 1,5406 Å a temperatura ambiente	Intensidad Pico relativa	Posición Pico (dos teta)	Intensidad Pico Relativa
5,69	Muy débil	21,06	Muy fuerte
6,76	Muy débil	21,29	Débil
8,38	Muy débil	22,31	Débil
11,43	Débil	23,02	Débil
12,74	Muy débil	23,66	Débil
13,62	Muy débil	24,18	Muy débil
14,35	Muy débil	24,98	Débil
15,09	Muy débil	25,50	Débil
15,66	Débil	26,23	Muy débil
16,43	Muy débil	26,46	Muy débil
17,16	Muy débil	27,59	Muy débil
17,66	Muy débil	28,89	Muy débil
18,31	Débil	29,58	Muy débil
19,03	Débil	30,32	Muy débil
19,54	Promedio	31,08	Muy débil
20,57	Débil	31,52	Muy débil

Tabla 2
Valores para Forma B

Posición Pico (dos teta) (CuK α λ = 1,5406 Å a temperatura ambiente	Intensidad Pico relativa	Posición Pico (dos teta)	Intensidad Pico Relativa
6,17	Muy débil	21,73	Promedio
10,72	Muy débil	22,48	Muy fuerte
12,33	Débil	23,34	Promedio
14,17	Débil	23,93	Promedio
14,93	Promedio	24,78	Promedio
15,88	Promedio	25,15	Débil
16,17	Promedio	25,90	Débil
17,11	Promedio	26,63	Promedio
17,98	Débil	27,59	Muy débil
19,01	Muy fuerte	28,66	Débil
19,61	Promedio	29,55	Débil
20,38	Promedio	30,49	Débil
21,55	Promedio	31,22	Débil

Las Figuras 5 a 7 son los resultados de la espectroscopia Raman de las Formas A, B y su mezcla, respectivamente, del análogo sujeto. Los espectros demuestran además dos distintas formas de cristales, en particular las bandas a $3\,130\text{ cm}^{-1}$ y $3\,115\text{ cm}^{-1}$.

Las características físicas de distinción de las dos formas de polimorfo se muestran en la Tabla 3 de abajo. La calorimetría de la solución se determinó usando Micro calorímetro Thermometrics en etanol a 25°C . Las solubilidades se determinaron similarmente a 25°C . Es adicionalmente evidente a partir de algunos de los datos, particularmente el calor de la solución, que la Forma A es la más estable y, consecuentemente, se prefiere la Forma A.

Tabla 3

Característica	Forma A	Forma B
Solubilidad en Agua	0,1254	0,1907
Solubilidad en 3% Polisorbato 80 (Acuoso)	0,2511	0,5799
Calor de la Solución	20,6 kJ/mol	9,86 kJ/mol

La Forma A y la Forma B de los análogos de epotilona representados por la fórmula I de arriba pueden caracterizarse adicionalmente por parámetros de célula unitaria obtenidos a partir de análisis cristalográfico de rayos X de un solo cristal tal como se establece abajo. Un conteo detallado de las células unitarias puede encontrarse en el Capítulo 3 de Stout & Jensen, Determinación de estructura de Rayos X: Una Guía Práctica, MacMillian Co., New York, NY (1968).

Parámetros de Célula Unitaria de Forma A

Dimensiones de Célula	$a = 14,152(6)\text{ \AA}$ $b = 30,72(2)\text{ \AA}$ $c = 6,212(3)\text{ \AA}$ Volumen = $2\,701(4)\text{ \AA}^3$
Espacio grupo	$P2_12_12_1$ Ortorhómbico
Moléculas/célula unitaria	4

Densidad (calculada)(g/cm ³)	1,247
Punto de Fusión	182-185°C (descomposición)

Parámetros de Célula Unitaria de Forma B

Dimensiones de Célula	a = 16,675 (2) Å b = 28,083(4) Å c = 6,054(1) Å Volumen = 2 835(1) Å ³
Espacio grupo	P2 ₁ 2 ₁ 2 ₁ Ortorhómbico
Moléculas/célula unitaria	4
Densidad (calculada) (g/cm ³)	1,187
Punto de fusión	191-199°C (descomposición)

Las diferencias entre las Formas A y B del análogo de epotilona sujeto se ilustran adicionalmente mediante las conformaciones de estado sólido de cada una tal como se ilustra en la Figura 8 y la Figura 9, respectivamente, basadas en las coordenadas atómicas fraccionales listadas en las Tablas 4 a 7 de abajo.

Tabla 4

Coordenadas Atómicas Fraccionales para el Análogo de epotilona de fórmula I: Forma A

Átomo	X	Y	Z	U11*10e2
C1	0,3879(3)	0,4352(1)	0,5503(9)	60(6)
O1	0,4055(2)	0,4300(1)	0,7435(5)	68(4)
C2	0,2864(3)	0,4340(1)	0,4675(7)	42(6)
C3	0,2696(3)	0,4210(1)	0,2325(7)	56(6)
O3	0,3097(2)	0,4550(1)	0,1027(5)	71(4)
C4	0,1615(3)	0,4154(1)	0,1852(7)	50(6)
C5	0,1289(3)	0,3732(1)	0,2895(8)	58(6)
O5	0,0935(3)	0,3748(1)	0,4713(6)	135(6)
C6	0,1343(3)	0,3296(1)	0,1769(8)	66(6)
C7	0,1503(3)	0,2921(1)	0,3353(8)	84(6)
O7	0,1410(3)	0,2528(1)	0,2127(6)	127(5)
C8	0,2449(4)	0,2936(1)	0,4540(8)	83(7)

C9	0,3284(4)	0,2824(1)	0,3072(9)	81(7)
C10	0,4258(4)	0,2877(1)	0,4141(8)	76(7)
C11	0,4467(3)	0,3359(1)	0,4622(8)	67(6)
C12	0,5220(3)	0,3426(1)	0,6294(8)	53(6)
O12	0,6171(2)	0,3288(1)	0,5612(5)	56(4)
C13	0,5983(3)	0,3746(1)	0,5991(8)	50(6)
C14	0,6099(3)	0,4053(1)	0,4113(8)	47(6)
C15	0,5568(3)	0,4477(1)	0,4538(8)	44(6)
N16	0,4552(3)	0,4426(1)	0,4005(6)	41(5)
C17	0,1482(4)	0,4138(2)	-0,0603(8)	103(7)
C18	0,1043(4)	0,4539(1)	0,2734(8)	62(6)
C19	0,0386(4)	0,3232(2)	0,0572(10)	92(8)
C20	0,2404(5)	0,2630(2)	0,6482(10)	145(9)
C21	0,4974(4)	0,3301(2)	0,8563(9)	109(8)
C22	0,5935(3)	0,4860(1)	0,3281(8)	48(6)
C23	0,5989(4)	0,4815(2)	0,0875(8)	132(8)
C24	0,6154(3)	0,5222(1)	0,4376(8)	59(6)
C25	0,6392(3)	0,5656(1)	0,3573(8)	61(6)
N26	0,6786(3)	0,5941(1)	0,5076(6)	75(6)
C27	0,6902(3)	0,6325(2)	0,4255(8)	59(6)
S28	0,6529(1)	0,6381(1)	0,1655(2)	92(2)
C29	0,6196(4)	0,5846(2)	0,1632(9)	85(7)
C30	0,7292(4)	0,6703(2)	0,5523(10)	106(8)

Tabla 4 Continuación

U22*10e2	U33*10e2	U12*10e2	U13*10e2	U23*10e2
25(4)	138(8)	-2(4)	16(5)	-9(4)
85(4)	100(5)	6(3)	4(3)	1(3)
64(5)	106(6)	0(4)	3(4)	-5(4)
44(5)	103(6)	-7(4)	5(4)	13(4)
58(3)	128(4)	-6(3)	18(3)	3(3)
63(5)	112(6)	-12(4)	-3(4)	7(4)
82(6)	103(7)	-6(4)	-13(5)	4(5)
83(4)	144(5)	-16(4)	39(4)	5(3)
71(5)	118(6)	-13(5)	-7(4)	-10(4)
43(5)	134(6)	-27(4)	-2(5)	-10(5)
61(4)	163(5)	-34(3)	-17(4)	-9(3)
56(5)	127(6)	-26(5)	-4(5)	3(5)
68(5)	153(7)	-1(5)	-4(5)	-26(5)
56(-5)	166(8)	13(5)	-19(5)	-15(5)
61(5)	126(7)	-3(4)	-19(4)	-5(5)
64(5)	138(7)	16(4)	8(5)	-1(5)
61(3)	155(4)	15(3)	8(3)	4(3)

45(5)	162(7)	3(4)	2(5)	-8(5)
63(5)	159(7)	2(4)	5(5)	7(5)
44(5)	143(6)	-4(4)	7(4)	-1(4)
65(4)	106(5)	-3(3)	6(3)	-2(3)
128(7)	104(7)	-29(6)	-10(5)	18(5)
67(5)	164(7)	17(5)	9(5)	12(5)
115(7)	217(10)	-17(6)	-70(7)	-19(7)
114(7)	158(8)	-34(6)	-20(6)	47(6)
92(6)	131(7)	19(5)	10(5)	8(5)
63(5)	122(6)	6(4)	4(5)	-1(5)
78(6)	116(7)	-7(5)	12(5)	-13(5)
55(5)	132(6)	-6(4)	9(5)	7(5)
65(5)	127(7)	-12(4)	8(5)	5(5)
58(5)	129(5)	-9(4)	4(4)	-5(4)
69(6)	128(6)	9(4)	2(5)	7(5)
79(1)	163(2)	-10(1)	-3(1)	20(1)
78(6)	161(8)	-13(5)	-9(6)	3(6)
75(6)	186(8)	-29(5)	-5(6)	-10(6)

Tabla 5

Posiciones de Hidrógeno: Forma A

Átomo	X	Y	Z	U*10e2
H21	0,2475(0)	0,4114(0)	0,5659(0)	4,86(0)
H22	0,2576(0)	0,4663(0)	0,4871(0)	4,86(0)
H31	0,3056(0)	0,3905(0)	0,2005(0)	4,59(0)
H3	0,3433(0)	0,4414(0)	-0,0241(0)	5,55(0)
H61	0,1951(0)	0,3304(0)	0,0646(0)	5,55(0)
H71	0,0960(0)	0,2932(0)	0,4607(0)	5,80(0)
H7	0,1332(0)	0,2276(0)	0,3158(0)	7,23(0)
H81	0,2588(0)	0,3266(0)	0,5107(0)	5,85(0)
H91	0,3274(0)	0,3037(0)	0,1672(0)	6,41(0)
H92	0,3217(0)	0,2491(0)	0,2527(0)	6,41(0)
H101	0,4802(0)	0,2743(0)	0,3130(0)	6,34(0)
H102	0,4253(0)	0,2697(0)	0,5663(0)	6,34(0)
H111	0,4687(0)	0,3519(0)	0,3132(0)	5,60(0)
H112	0,3823(0)	0,3519(0)	0,5172(0)	5,60(0)
H131	0,6275(0)	0,3905(0)	0,7410(0)	5,60(0)
H141	0,6837(0)	0,4117(0)	0,3814(0)	5,88(0)
H142	0,5803(0)	0,3901(0)	0,2659(0)	5,88(0)
H151	0,5638(0)	0,4542(0)	0,6281(0)	5,35(0)
H 16	0,4353(0)	0,4447(0)	0,2429(0)	4,88(0)
H171	0,1722(0)	0,4437(0)	-0,1367(0)	6,90(0)
H172	0,1919(0)	0,3871(0)	-0,1308(0)	6,90(0)

H173	0,0763(0)	0,4077(0)	-0,1076(0)	6,90(0)
H181	0,1273(0)	0,4835(0)	0,1956(0)	6,31(0)
H182	0,0295(0)	0,4491(0)	0,2355(0)	6,31(0)
H183	0,1123(0)	0,4566(0)	0,4436(0)	6,31(0)
H191	0,0370(0)	0,2923(0)	-0,0226(0)	8,78(0)
H192	-0,0186(0)	0,3233(0)	0,1794(0)	8,78(0)
H193	0,0259(0)	0,3491(0)	-0,0525(0)	8,78(0)
H201	0,3050(0)	0,2635(0)	0,7355(0)	8,17(0)
H202	0,1828(0)	0,2733(0)	0,7536(0)	8,17(0)
H203	0,2252(0)	0,2304(0)	0,5923(0)	8,17(0)
H211	0,4260(0)	0,3415(0)	0,8951(0)	6,84(0)
H212	0,4998(0)	0,2955(0)	0,8754(0)	6,84(0)

Tabla 6

Coordenadas Atómicas Fraccionales para el Análogo de epotilona de fórmula I: Forma B

Átomo	X	Y	Z	U11*10e2
C1	0,2316(2)	0,1043(2)	0,7342(8)	56(4)
O1	0,2321(2)	0,1159(1)	0,5376(5)	131(4)
C2	0,1812(2)	0,0623(1)	0,8106(7)	62(4)
C3	0,1535(2)	0,0622(1)	1,0506(7)	52(4)
O3	0,2226(2)	0,0539(1)	1,1856(5)	65(3)
C4	0,0876(2)	0,0237(1)	1,0903(7)	63(4)
C5	0,0096(2)	0,0415(1)	0,9838(8)	57(4)
O5	-0,0132(2)	0,0252(1)	0,8117(6)	100(4)
C6	-0,0409(2)	0,0796(1)	1,1023(6)	53(4)
C7	-0,0754(2)	0,1151(1)	0,9373(9)	60(4)
O7	-0,1316(2)	0,1434(1)	1,0606(7)	79(3)
C8	-0,0135(3)	0,1468(1)	0,8213(8)	75(5)
C9	0,0274(2)	0,1817(1)	0,9812(9)	80(5)
C10	0,0946(3)	0,2107(2)	0,8766(10)	95(5)
C11	0,1389(3)	0,2407(2)	1,0447(11)	97(5)
C12	0,2065(3)	0,2688(2)	0,9440(11)	110(6)
O12	0,2653(2)	0,2862(1)	1,1070(8)	124(4)
C13	0,2894(3)	0,2520(2)	0,9406(10)	104(6)
C14	0,3190(3)	0,2049(2)	1,0281(10)	117(6)
C15	0,3253(3)	0,1676(1)	0,8388(8)	86(5)
N16	0,2738(2)	0,1273(1)	0,8901(7)	64(4)
C17	0,0762(3)	0,0176(2)	1,3416(8)	102(6)
C18	0,1109(2)	-0,0244(1)	0,9909(8)	82(5)
C19	-0,1098(3)	0,0529(2)	1,2197(10)	79(5)
C20	-0,0528(3)	0,1729(2)	0,6272(9)	149(7)
C21	0,1829(4)	0,3056(2)	0,7748(15)	175(9)

C22	0,4128(3)	0,1527(2)	0,7991(8)	80(5)
C23	0,4521(4)	0,1784(3)	0,6109(13)	141(8)
C24	0,4477(3)	0,1216(2)	0,9319(9)	88(5)
C25	0,5303(3)	0,1032(2)	0,9346(9)	76(5)
N26	0,5822(2)	0,1091(2)	0,7577(8)	71(5)
C27	0,6498(3)	0,0890(2)	0,7986(10)	98(6)
S28	0,6565(1)	0,0612(1)	1,0487(3)	107(1)
C29	0,5605(3)	0,0785(2)	1,1053(10)	93(6)
C30	0,7206(4)	0,0891(3)	0,6410(12)	102(7)

Tabla 6 Continuación

U22*10e2	U33*10e2	U12*10e2	U13*10e2	U23*10e2
74(5)	86(6)	5(4)	-6(4)	-16(5)
88(3)	74(4)	-24(3)	-13(3)	-7(3)
85(5)	68(5)	-7(4)	-6(4)	-22(5)
67(4)	71(5)	1(3)	-19(4)	-6(4)
123(4)	96(4)	7(3)	-29(3)	-19(4)
75(4)	63(5)	5(4)	-4(4)	-10(4)
61(4)	78(5)	-7(3)	-2(4)	-10(4)
3(4)	100(4)	19(3)	-38(3)	-38(4)
77(4)	92(6)	14(4)	2(5)	-17(5)
111(4)	185(5)	40(3)	22(4)	-10(4)
74(5)	106(6)	4(4)	8(5)	-14(5)
69(4)	136(7)	-10(4)	-1(5)	-19(5)
89(5)	175(8)	-21(4)	15(7)	-27(6)
98(6)	191(9)	-22(5)	27(7)	-48(7)
64(5)	208(9)	-16(5)	10(7)	-28(6)
98(4)	241(7)	-36(3)	30(5)	-77(5)
82(5)	169(9)	-25(5)	23(6)	-38(6)
102(6)	160(8)	-3(5)	-26(6)	-53(6)
74(5)	107(6)	-18(4)	-17(5)	-15(5)
100(4)	98(5)	-26(3)	-13(4)	-19(4)
129(6)	66(5)	-13(5)	-5(5)	10(5)
58(4)	113(6)	13(4)	-11(5)	-9(5)
139(7)	187(9)	1(5)	54(6)	29(7)
116(6)	123(8)	10(6)	-19(6)	22(6)
86(6)	338(15)	-8(6)	0(11)	21(9)
80(5)	108(6)	-29(4)	-5(5)	-6(5)
261(11)	237(13)	28(8)	54(9)	146(11)
111(6)	111(7)	-5(5)	3(5)	21(6)
96(5)	119(7)	-12(4)	2(5)	-2(6)
192(7)	114(6)	2(5)	-6(5)	3(6)
165(7)	125(7)	-5(6)	-13(6)	-19(7)
128(2)	173(2)	12(1)	-25(2)	0(2)

122(6)	166(9)	4(5)	3(6)	43(7)
443(17)	150(10)	45(10)	18(7)	-17(12)

Tabla 7

Posiciones de Hidrógeno: Forma B

Átomo	X	Y	Z	U*10e2
H21	0,1283(0)	0,0616(0)	0,7084(0)	4,86(0)
H22	0,2159(0)	0,0306(0)	0,7857(0)	4,86(0)
H31	0,1272(0)	0,0969(0)	1,0910(0)	4,51(0)
H3	0,2243(0)	0,0785(0)	1,3075(0)	6,11(0)
H61	-0,0043(0)	0,0983(0)	1,2199(0)	4,99(0)
H71	-0,1059(0)	0,0964(0)	0,8057(0)	5,69(0)
H7	-0,1609(0)	0,1655(0)	0,9542(0)	7,62(0)
H81	0,0313(0)	0,1244(0)	0,7484(0)	5,58(0)
H91	-0,0180(0)	0,2062(0)	1,0453(0)	6,10(0)
H92	0,0520(0)	0,1619(0)	1,1189(0)	6,10(0)
H101	0,1365(0)	0,1874(0)	0,7953(0)	7,47(0)
H102	0,0691(0)	0,2349(0)	0,7527(0)	7,47(0)
H111	0,0976(0)	0,2651(0)	1,1204(0)	7,74(0)
H112	0,1633(0)	0,2170(0)	1,1686(0)	7,74(0)
H131	0,3308(0)	0,2613(0)	0,8107(0)	7,31(0)
H141	0,3779(0)	0,2094(0)	1,1016(0)	7,61(0)
H142	0,2780(0)	0,1920(0)	1,1530(0)	7,61(0)
H151	0,3046(0)	0,1836(0)	0,6859(0)	5,74(0)
H16	0,2693(0)	0,1161(0)	1,0487(0)	5,71(0)
H171	0,0304(0)	-0,0088(0)	1,3753(0)	6,33(0)
H172	0,1318(0)	0,0064(0)	1,4171(0)	6,33(0)
H173	0,0577(0)	0,0512(0)	1,4165(0)	6,33(0)
H181	0,0633(0)	-0,0501(0)	1,0184(0)	5,58(0)
H182	0,1192(0)	-0,0207(0)	0,8122(0)	5,58(0)
H183	0,1655(0)	-0,0370(0)	1,0628(0)	5,58(0)
H191	-0,1481(0)	0,0774(0)	1,3099(0)	8,04(0)
H192	-0,1459(0)	0,0330(0)	1,1036(0)	8,04(0)
H193	-0,0849(0)	0,0274(0)	1,3402(0)	8,04(0)
H201	-0,0094(0)	0,1955(0)	0,5429(0)	7,89(0)
H202	-0,0763(0)	0,1475(0)	0,5059(0)	7,89(0)
H203	-0,1024(0)	0,1951(0)	0,6816(0)	7,89(0)
H211	0,1596(0)	0,2886(0)	0,6259(0)	11,47(0)
H212	0,1382(0)	0,3292(0)	0,8404(0)	11,47(0)
H213	0,2355(0)	0,3265(0)	0,7267(0)	11,47(0)
H231	0,5051(0)	0,1602(0)	1,0559(0)	6,57(0)
H291	0,5291(0)	0,0702(0)	1,2584(0)	7,73(0)
H301	0,7003(0)	0,0920(0)	0,4744(0)	13,05(0)

H302	0,7623(0)	0,1165(0)	0,6811(0)	13,05(0)
H303	0,7525(0)	0,0542(0)	0,6572(0)	13,05(0)

Basado en los anteriores datos, se concluye que las Formas A y B son únicas entidades cristalinas.

Los siguientes ejemplos no limitativos sirven para ilustrar la práctica de la invención.

Ejemplo 1

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihidroxi-8,8,10,12,16-pentametil-3-[1-metil-2-(2-metil-4-tiazolil)etenil]-4-aza-17-oxabicyclo [14.1.0]heptadecano-5,9-diona.

A un frasco de fondo redondo encamisado de 125 mL, ajustado con un agitador mecánico, se combinó epotilona-B (5,08g), tetrabutylamonio ázido (Bu_4NN_3) (3,55g, 1,25 equivalentes), cloruro de amonio (1,07g, 2 equivalentes), agua (1,8 ml, 10 equivalentes), tetrahidrofuran (THF) (15 ml), y N,N-dimetilformamida (DMF) (15 ml). La mezcla se sometió a inercia esparciendo sub-superficie de nitrógeno durante 15 minutos. En un segundo frasco se cargó tetrahidrofuran (70 ml), seguido por trimetilfosfina (PMe_3) (1,56 ml, 1,5 equivalentes), luego aducto de tris(dibenzilideno acetona)-di-paladio(O)cloroformo ($\text{Pd}_2(\text{dba})_3\text{CHCl}_3$) (0,259 g, 0,025 equivalentes). La mezcla de catalizador se agitó durante 20 minutos a temperatura ambiente, luego se agregó a la mezcla de epotilona-B. La mezcla combinada se agitó durante 4,5 horas a 30°C. La mezcla de la reacción completada se filtró entonces para retirar el cloruro de amonio sólido (NH_4Cl). El filtrado contenía (BS, ϵR , ξS , ηS , 2R, 3S)-3-[(2S, 3E)-2-amino-3-metil-4-(2-metil-4-tiazolil)-3-butenil]- β,ξ -dihidroxi- γ ,

γ , ϵ , η , 2-pentametil- δ -oxooxirano ácido undecanóico, sal de tetrabutylamonio (1:1) con un área de HPLC de 94,1%.

En un frasco de 500 mL se combinó 1-[3-(dimetilamino)propil]-3-etilcarbodiimida hidrocloreuro (EDCI) (3,82 g, 2 equivalentes), 1-hidroxi-7-benzotriazolo hidrato (HOBt) (1,68g, 1,1 equivalentes), carbonato de potasio (1,38 g, 1 equivalente), N, N-dimetilformamida (DMF) (40 ml) y tetrahidrofuran (THF) (160 ml). La mezcla se calentó a 35°C y el filtrado de arriba se agregó allí, gota a gota durante un periodo de tres horas. Esta mezcla se agitó entonces durante 1 hora adicional a 35°C. Se aplicó destilación por vacío entonces a la mezcla de la reacción para reducir su volumen a alrededor de 80 mL. La solución resultante se partió entre 100 mL de acetato de etilo y 100 mL de agua. La capa acuosa se extrajo entonces en retroceso con 100 ml acetato de etilo. Las capas orgánicas combinadas se extrajeron con 50 ml de agua y luego 20 mL de salmuera. La solución del producto resultante se filtró a través de una almohadilla Zeta Plus® y luego se laminó a un aceite. El aceite crudo se disolvió en diclorometano (20 mL) y se lavó con agua para retirar las trazas finales de solventes de síntesis y se laminó como un sólido. El sólido crudo se sometió a cromatografía sobre gel de sílice 60 (35 ml de sílice por gramo de producto teórico) con un levigado compuesto de 88% diclorometano (CH_2Cl_2), 10% a 30% de acetato de etilo (EtOAc) y 2% de trietilamina (Et_3N). Las fracciones se analizaron por HPLC, cuyas de mayor pureza se combinaron y laminaron para dar el sólido purificado. El sólido resultante, aproximadamente 2 g, se precipitó en acetato de etilo (32 ml) durante 40 minutos a 75°C, luego ciclohexano (C_6H_{12}) (16 ml) se agregó lentamente, y la mezcla se enfrió a 5°C. El sólido purificado se recogió sobre papel de filtro, se lavó con acetato de etilo/ ciclohexano frío, y se secó. El obtenido fue 1,72 g (38% obtenido) del producto sólido blanco, [1S-

[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]-7,11-dihidroxi-8,8,10,12,16-pentametil-3-[1-metil-2-(2-metil-4-tiazolil)etenil]-4-aza-17-oxabicyclo[14.1.0]heptadecano-5,9-diona, con un área de HPLC de 99,2%.

Ejemplo 2

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]-7,11-Dihidroxi-8,8,10,12,16-pentametil-3-[1-metil-2-(2-metil-4-tiazolil)etenil]-4-aza-17-oxabicyclo[14.10]heptadecano-5,9-diona, Forma A.

Un frasco de tres cuellos de 250 mL se cargó con 0,61 g del compuesto titulado que ha sido purificado (filtración de almohadilla de gel de sílice con EtOAc/ hexano/ Et₃N como levigado, área de HPLC de 96,88) y acetato de etilo (28 mL, 46 ml/1g). El precipitado resultante se calentó a 75°C. Todos los sólidos se disolvieron después de que el precipitado se agitó a 75°C durante 60 minutos. La solución lograda se enfrió desde 75°C a 50°C durante 120 minutos, agregándose cristales de semilla de Forma A a 60°C. Los cristales aparecieron a 55°C. La temperatura se enfrió a 20°C posteriormente durante 120 minutos, mientras se agregó ciclohexano (35 mL, 57 mL/1 g) gota a gota a la mezcla durante un periodo de 60 minutos. El precipitado obtenido se enfrió a -10°C durante 120 minutos, y se mantuvo durante adicionales 60 minutos. El precipitado se filtró y los cristales blancos logrados se secaron para dar 0,514 g del compuesto titulado, Forma A, en 84,3% de obtenido con un área de HPLC de 99,4.

Forma A - Procedimiento alternativo

Un frasco de tres cuellos de 250 mL se cargó con 0,51 g del compuesto titulado que había sido purificado (filtración por almohadilla de gel de sílice con EtOAc/ hexano/ Et₃N como el levigado, área de HPLC de

96) y acetato de etilo (8,5 mL, 16,7 mL/g). El precipitado resultante se calentó a 80°C. La solución lograda se enfrió desde 80°C a 70°C durante 60 minutos, agregándose cristales de semilla de Forma A, a 70°C. La temperatura se enfrió posteriormente a 30°C durante 180 minutos. Los cristales aparecieron a 65°C. La solución se enfrió adicionalmente a -10°C durante 180 minutos, mientras ciclohexano (10,2 mL, 20 mL/g) se agregó gota a gota a la mezcla durante un periodo de 30 minutos. El precipitado obtenido se enfrió manteniendo durante adicionales 60 minutos. El precipitado se filtró y los cristales blancos obtenidos se secaron para dar 0,43 g del compuesto titulado, Forma A, en 84,3% de obtenido con un área de HPLC de 99,7.

Forma A - Procedimiento alternativo

Un frasco de tres cuellos de 500 mL se cargó con 18,3 g de una mezcla de Formas A y B que ha sido purificada (filtración por almohadilla de gel de sílice con EtOAc/ diclorometano/ Et₃N como el levigado, área de HPLC de 99) y acetato de etilo (183 mL, 10 mL/g). El precipitado resultante se calentó a 75°C, se agregaron cristales de semilla de Forma A y la temperatura se mantuvo durante 30 minutos. Ciclohexano (90,2 mL, 5 mL/g) se agregó gota a gota a la mezcla manteniendo la temperatura a 70°C. Después de completar la adición, la temperatura se descendió a 20°C y la mezcla se mantuvo con agitación durante adicionales 18 horas. La temperatura se descendió posteriormente a 5°C y se mantuvo durante 5 horas. El precipitado se filtró y los cristales blancos logrados se secaron para dar 16,1 g del compuesto titulado, Forma A, en 88% de obtenido con un área de HPLC de 99,49.

Ejemplo 3

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihidroxi-8,8,10,12,16-pentametil-3-[1-metil-2-(2-metil-4-tiazolil)etenil]-4-aza-17-oxabicyclo[14.1.0]heptadecano-5,9-diona, Forma B.

Un frasco de tres cuellos de 250 mL se cargó con 0,108 g del compuesto titulado que no ha sido purificado como en el Ejemplo 2, N,N-dimetilformamida (0,0216 g) y acetato de etilo (5 mL, 46 mL/1 g). El precipitado resultante se calentó a 80°C y agitó durante 30 minutos para disolver todos los sólidos. La solución lograda se enfrió desde 80°C a 30°C durante 120 minutos, los cristales aparecieron a 38°C. Ciclohexano (7,5 mL, 69,5 mL/1 g) se agregó gota a gota a la mezcla durante un periodo de 30 minutos mientras la temperatura se enfrió a -10°C durante 60 minutos, y se mantuvo durante adicionales 120 minutos. El precipitado se filtró y los cristales blancos obtenidos se secaron para dar 0,082 g del compuesto titulado, Forma B, en 76% de obtenido con un área de HPLC de 99,6.

Forma B - Procedimiento alternativo

Un frasco de tres cuellos de 250 mL se cargó con 0,458 g del compuesto titulado que no ha sido purificado como en el Ejemplo 2 y contenía alrededor de 6% de N,N-dimetilformamida y acetato de etilo (10 mL, 21,8 mL/1 g). El precipitado resultante se calentó a 78°C y se agitó durante 30 minutos para disolver todos los sólidos. La solución lograda se enfrió desde 78°C a 10°C durante 120 minutos. Se agregaron cristales de semilla de Forma A, a 10°C. Ciclohexano (20 mL, 43,7 mL/1 g) se agregó gota a gota a la mezcla durante un periodo de 60 minutos mientras la temperatura se enfrió a -10°C durante 120 minutos, y se mantuvo durante adicionales 120 minutos. El precipitado se filtró y los cristales blancos

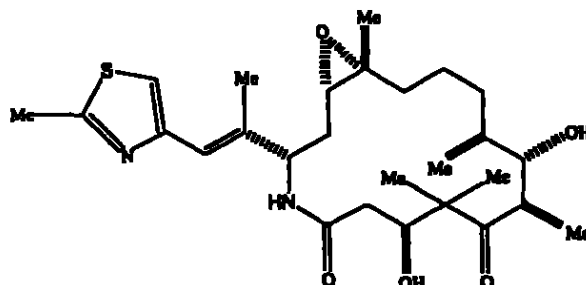
obtenidos se secaron para dar 0,315 g del compuesto titulado, Forma B, en 68.8% de obtenido con un área de HPLC de 98,2.

Forma B - Procedimiento alternativo

Una botella Wheaton de 5 mL se cargó con 250 mg del compuesto titulado que no ha sido purificado como en el Ejemplo 2 y tolueno (3,75 mL, 15 mL/ g.) y el precipitado resultante se calentó a 75°C y se mantuvo durante 30 minutos. La suspensión resultante se dejó enfriar a 20°C y se mantuvo a esa temperatura durante 18 horas con agitación. El precipitado se filtró y los cristales blancos obtenidos se secaron para dar 150 mg. del compuesto titulado, Forma B, en 60% de obtenido con un área de HPLC de 99,2

Reivindicamos:

1. Un polimorfo cristalino de un análogo de epotilona representado por la fórmula



I

que comprende Forma A caracterizada por:

parámetros de célula unitaria aproximadamente iguales a lo siguiente:

Dimensiones de Célula	$a = 14,152(6) \text{ \AA}$ $b = 30,72(2) \text{ \AA}$ $c = 6,212(3) \text{ \AA}$ $\text{Volumen} = 2\,701(4) \text{ \AA}^3$
Espacio grupo	$P2_12_12_1$ Ortorhómbico
Moléculas/célula unitaria	4
Densidad (calculada)(g/cm ³)	1,247
Punto de Fusión	182-185°C (descomposición)

picos característicos en el patrón de difracción de rayos x en polvo a valores de dos teta ($\text{CuK}\alpha \lambda = 1,5406 \text{ \AA}$ a 22°C: 5,69, 6,76, 8,38, 11,43, 12,74, 13,62, 14,35, 15,09, 15,66, 16,43, 17,19, 17,66, 18,31, 19,03, 19,54, 20,57, 21,06, 21,29, 22,31, 23,02, 23,66, 24,18, 24,98, 25,50, 26,23, 26,23, 26,46, 27,59, 28,89, 29,58, 30,32, 31,08 y 31,52; o

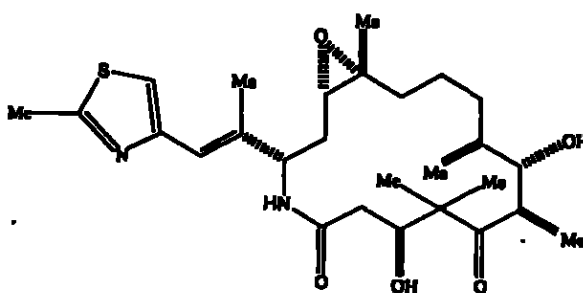
Forma caracterizada por:

parámetros de célula unitaria aproximadamente iguales a lo siguiente:

Dimensiones de Célula	a = 16,675 (2) Å b = 28,083 (4) Å c = 6,054 (1) Å Volumen = 2 835(1) Å ³
Espacio grupo	P2 ₁ 2 ₁ 2 ₁ Ortorhómbico
Moléculas/célula unitaria	4
Densidad (calculada) (g/cm ³)	1,187
Punto de fusión	191-199°C descomposición y

picos característicos en el patrón de difracción de rayos x en polvo a valores de dos theta (CuKα λ=1,5406 Å a 22°C: 6,17, 10,72, 12,33, 14,17, 14,93, 15,88, 16,17, 17,11, 17,98, 19,01, 19,61, 20,38, 21,55, 21,73, 22,48, 23,34, 23,93, 24,78, 25,15, 25,90, 26,63, 27,59, 28,66, 29,55, 30,49 y 31,22.

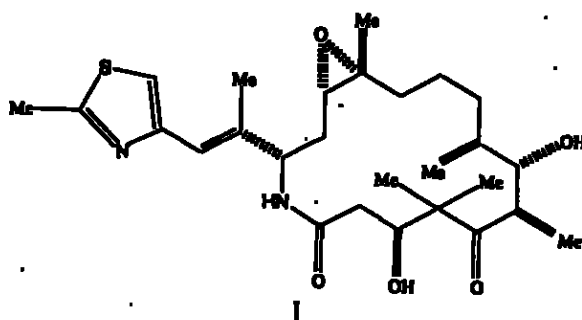
2. Un polimorfo cristalino de un análogo de epotilona representado por la fórmula



I...

que comprende Forma A caracterizada por difracción de rayos x en polvo sustancialmente como se muestra en la Figura 1 y un espectro Raman como se muestra sustancialmente en la Figura 5; o una Forma B caracterizada por difracción de rayos x en polvo como se muestra en la Figura 2 y un espectro Raman sustancialmente como se muestra en la Figura 6.

3. Un polimorfo cristalino de un análogo de epotilona representado por la fórmula



que comprende Forma A caracterizada por una solubilidad en agua de 0,1254, una solubilidad en una solución acuosa al 3% de polisorbato 80 de 0,2511, un punto de fusión con descomposición entre 182-185°C y un calor de solución de 20,6 kJ/mol; o Forma B caracterizada por una solubilidad en agua de 0,1907, una solubilidad en una solución acuosa al 3% de polisorbato 80 de 0,5799, un punto de fusión con descomposición entre 191-199°C y un calor de solución de 9,86 kJ/mol.

4. Un polimorfo cristalino de acuerdo con las Reivindicaciones 1, 2 o 3, donde dicho polimorfo es Forma A.

5. Un polimorfo cristalino de acuerdo con las Reivindicaciones 1, 2 o 3, donde dicho polimorfo es Forma B.
6. Un material cristalino que comprende una mezcla de Forma A y Forma B de acuerdo con la Reivindicación 1, 2 o 3.
7. Un proceso para producir un polimorfo cristalino que es Forma A del análogo de epotilona representado por la fórmula I en la Reivindicación 1 que comprende calentar un precipitado de dicho análogo representado por la fórmula I en desde alrededor de 8 a alrededor de 16 mL de acetato de etilo por gramo de dicho análogo a alrededor de 75°C manteniendo la temperatura durante alrededor de una hora, agregando una cantidad de ciclohexano en una relación con respecto a la cantidad de acetato de etilo de desde alrededor de 1:2 a alrededor de 2:2, permitiendo que la mezcla se enfríe a temperatura ambiente, manteniendo la mezcla con agitación desde alrededor de 12 a 96 horas, enfriándola adicionalmente a alrededor de 5°C durante alrededor de dos horas y recuperando la Forma A cristalina de allí.
8. Un proceso de acuerdo con la Reivindicación 7 donde la cantidad de ciclohexano agregada está en una relación 1:2 con respecto a la cantidad de acetato de etilo utilizada para formar dicho precipitado.
9. Un proceso de acuerdo con la Reivindicación 7, donde dicho precipitado de dicho análogo representado por la fórmula I en acetato de etilo se calienta a alrededor de 75°C cristales de semilla son agregados allí y la mezcla se mantiene durante alrededor de 30 minutos después de lo cual dicha cantidad de ciclohexano se agrega allí mientras se mantiene la mezcla a alrededor de 70°C, enfriando la mezcla a temperatura ambiente,

manteniendo la mezcla con agitación durante alrededor de 18 horas, enfriándola adicionalmente a alrededor de 5°C durante alrededor de dos horas y recuperando de allí la Forma A cristalina.

10. Un proceso de acuerdo con la Reivindicación 7, donde dicho precipitado de dicho análogo representado por la fórmula I en acetato de etilo se calienta a una cantidad de 75°C durante por lo menos una hora hasta que se forma una solución, enfriando dicha solución a alrededor de 50°C durante alrededor de dos horas, agregando allí dichos cristales de semilla cuando la temperatura alcanza alrededor de 60°C, enfriando la solución a alrededor de 30°C durante alrededor de tres horas, reduciendo adicionalmente la temperatura de la solución a -10°C durante alrededor de tres horas durante una hora donde dicha cantidad de ciclohexano se agrega allí gota a gota, manteniendo la mezcla resultante a -10°C durante alrededor de una hora y recuperando de allí la Forma A cristalina.

11. Un proceso para producir un polimorfo cristalino que es Forma B del análogo de epotilona representado por la fórmula I en la Reivindicación 1 que comprende calentar un precipitado de dicho análogo representado por la fórmula I en desde alrededor de 40 a alrededor de 50 mL de acetato de etilo por gramo de dicho análogo a alrededor de 75°C a 80°C, manteniendo la temperatura durante alrededor de una hora formando así una solución, manteniendo la solución a temperatura durante alrededor de 30 minutos, enfriando la solución a alrededor de 30°C durante alrededor de dos horas, reduciendo adicionalmente la temperatura de la solución a -10°C durante alrededor de una hora durante la cual una cantidad de ciclohexano en una relación con respecto a la cantidad de acetato de etilo de desde alrededor de 1:2 hasta alrededor de 2:2 se agrega allí gota a gota durante un periodo de alrededor de treinta minutos,

manteniendo la mezcla resultante a -10°C durante alrededor de dos horas y recuperando de allí la Forma B cristalina.

12. Un proceso de acuerdo con la Reivindicación 11, donde dicho precipitado de dicho análogo representado por la fórmula I en acetato de etilo se calienta a alrededor de 78°C formando así una solución, enfriando la solución a alrededor de 10°C durante alrededor de dos horas, agregando cristales de semilla cuando la temperatura alcanza 10°C , reduciendo adicionalmente la temperatura de la solución a -10°C durante alrededor de dos horas durante la cual dicha cantidad de ciclohexano se agrega allí gota a gota durante un periodo de alrededor de treinta minutos, manteniendo la mezcla resultante a -10°C durante alrededor de dos horas y recuperando de allí la Forma B cristalina.

13. Un proceso para producir un polimorfo cristalino que es Forma B del análogo de epotilona representado por la fórmula I en la Reivindicación 1 que comprende calentar un precipitado de dicho análogo representado por la fórmula I en desde alrededor de 10 a alrededor de 20 mL de tolueno por gramo de dicho análogo a alrededor de 75°C a 80°C , manteniendo la temperatura durante alrededor de 30 minutos, enfriando la mezcla a alrededor de 20°C , manteniendo la temperatura durante alrededor de 18 horas con agitación y recuperando de allí la Forma B cristalina.

14. Una composición farmacéutica que comprende como un ingrediente activo una cantidad efectiva de un polimorfo cristalino como se reivindicó en las Reivindicaciones 1, 2 o 3 y uno o más de sus portadores, excipientes o diluyentes farmacéuticamente aceptables

15. Una composición farmacéutica de acuerdo con la Reivindicación 14, donde dicho polimorfo cristalino es Forma A.

16. Una composición farmacéutica de acuerdo con la Reivindicación 14, donde dicho polimorfo cristalino es Forma B.

17. Una composición farmacéutica de acuerdo con la Reivindicación 14, donde dicho polimorfo cristalino es una mezcla de Forma A y Forma B.

18. Un método para el tratamiento del cáncer u otras enfermedades proliferativas que comprende administrar a un mamífero en necesidad de él una cantidad efectiva de un polimorfo cristalino como se reivindicó en las Reivindicaciones 1, 2 o 3.

19. Un método de acuerdo con la Reivindicación 18, donde dicho polimorfo cristalino es Forma A.

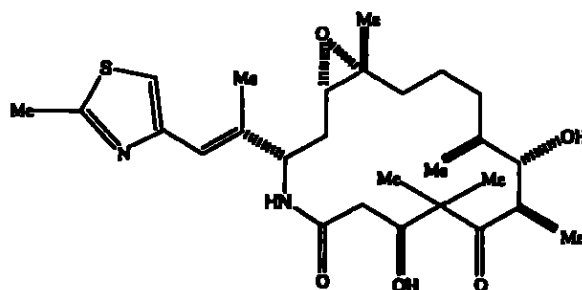
20. Un método de acuerdo con la Reivindicación 18, donde dicho polimorfo cristalino es Forma B.

21. Un método de acuerdo con la Reivindicación 18, donde dicho polimorfo cristalino se administra en forma parenteral.

POLIMORFOS DE UN ANÁLOGO DE EPOTILONA

Extracto de la Invención

Se proporcionan de acuerdo con la presente invención dos polimorfos cristalinos, designados Forma A y Forma B, respectivamente, así como sus mezclas, de un análogo de epotilona representado por la fórmula



I

También se proporcionan métodos de formar los novedosos polimorfos, métodos terapéuticos que los utilizan y formas de dosificación farmacéutica que los contienen.

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

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
21 February 2002 (21.02.2002)

PCT

(10) International Publication Number
WO 02/14323 A2

(51) International Patent Classification: C07D 491/00

FAVREAU, Denis [CA/US]; 5065 Terrasse Beaudry,
Saint-Hubert, Quebec J3Y 6L2 (CA).

(21) International Application Number: PCT/US01/24540

(22) International Filing Date: 1 August 2001 (01.08.2001)

(74) Agents: ALGIERI, Aldo et al.; Bristol-Myers Squibb
Company, Lawrenceville-Princeton Road, P.O. Box 4000,
Princeton, NJ 08543-4000 (US).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/225,590 16 August 2000 (16.08.2000) US(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, GR, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
ZW.(71) Applicant (for all designated States except US):
BRISTOL-MYERS SQUIBB COMPANY [US/US];
Lawrenceville-Princeton Road, P.O. Box 4000, Princeton,
NJ 08543-4000 (US).(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG).

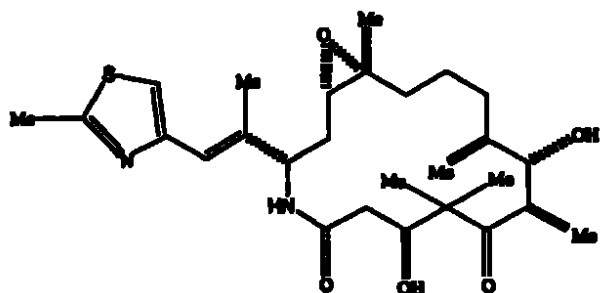
(72) Inventors; and

(75) Inventors/Applicants (for US only): DIMARCO, John,
D. [US/US]; 16 Neal Drive, East Brunswick, NJ 08816
(US). GUGGOUTAS, Jack, Z. [US/US]; 101 Westerly
Road, Princeton, NJ 08540 (US). VITEZ, Imre, M.
[US/US]; 117 Main Street, Whitehouse Station, NJ 08889
(US). DAVIDOVICH, Martha [US/US]; 159 Fern Road,
East Brunswick, NJ 08816 (US). GALELLA, Michael
[US/US]; 3 Evergreen Court, Belle Mead, NJ 08502 (US).
MALLOY, Timothy, M. [US/US]; 1902 Wakefield Road,
Yardley, PA 19067 (US). GUO, Zhenrong [CA/US];
21 Augusta Place, East Brunswick, NJ 08816 (US).

Published:

— without international search report and to be republished
upon receipt of that reportFor two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: POLYMORPHS OF AN EPOTHILONE ANALOG



(I)

(57) Abstract: There are provided in accordance
with the present invention two crystalline
polymorphs, designated Form A and Form B,
respectively, as well as mixtures thereof, of an
epothilone analog represented by formula (I).
Also provided are methods of forming the novel
polymorphs, therapeutic methods utilizing them and
pharmaceutical dosage forms containing them.

WO 02/14323 A2

POLYMORPHS OF AN EPOTHILONE ANALOG

5

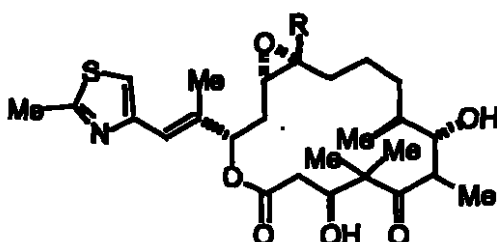
Field of the Invention

The present invention relates to crystalline polymorphic forms of a highly potent epothilone analog that is characterized by enhanced properties.

10

Background of the Invention

Epithilones are macrolide compounds that find utility in the pharmaceutical field. For example, Epithilones A and B having the structures:



Epothilone A $R=H$

Epothilone B **R=Me**

may be found to exert microtubule-stabilizing effects similar to paclitaxel (TAXOL[®]) and hence cytotoxic activity against rapidly proliferating cells, such as, tumor cells or other hyperproliferative cellular disease, see Hofle, G., *et al.*, Angew. Chem. Int. Ed. Engl., Vol. 35, No.13/14, 1567-1569 (1996); WO93/10121 published May 27, 1993; and WO97/19086 published May 29, 1997.

Various epothilone analogs have been synthesized and may be used to treat a variety of cancers and other abnormal proliferative diseases. Such analogs are disclosed in Hofle *et al.*, *Id.*; Nicolaou, K.C., *et al.*, Angew Chem. Int. Ed. Engl., Vol. 36, No. 19, 2097-2103 (1997); and Su, D.-S., *et al.*, Angew Chem. Int. Ed. Engl., Vol. 36, No. 19, 2093-2097 (1997).

A particularly advantageous epothilone analog that has been found to have advantageous activity is [1S- [1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione. In accordance with the present invention, two crystal forms of the subject epothilone analog are provided. These polymorphs, which have been designated as Forms A and B, respectively, are novel crystal forms and are identified hereinbelow.

Brief Description of the Drawings

10

FIG. 1 is a powder x-ray diffraction pattern (CuK α λ =1.5406 Å at room temperature) of Form A of the subject epothilone analog.

FIG. 2 is a powder x-ray diffraction pattern of Form B (Cu K α λ =1.5406 Å at room temperature) of the subject epothilone analog.

15

FIG. 3 is a powder x-ray diffraction pattern of a mixture of Forms A and B (Cu K α λ =1.5406 Å at room temperature) of the subject epothilone analog.

FIG. 4 is a comparison of the simulated and actual powder x-ray diffraction patterns of Forms A and B of the subject epothilone analog.

FIG. 5 is a Raman spectrum of Form A of the subject epothilone analog.

20

FIG. 6 is a Raman spectrum of Form B of the subject epothilone analog.

FIG. 7 is a Raman spectrum of a mixture of Forms A and B of the subject epothilone analog.

FIG. 8 depicts the solid state conformation in Form A of the subject epothilone analog.

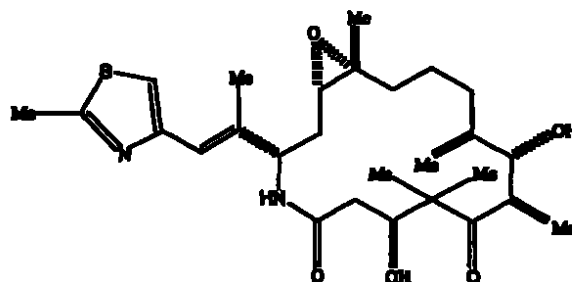
25

FIG. 9 depicts the solid state conformation in Form B of the subject epothilone analog.

Summary of the Invention

041

In accordance with the present invention, there are provided two crystalline polymorphs of the epothilone analog represented by formula I.

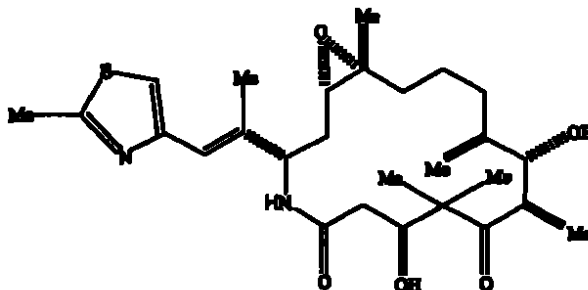


I

One of these polymorphs, designated Form A, has been found to have particularly advantageous properties. The present invention is directed to crystalline polymorphs Form A and Form B as well as mixtures thereof. The present invention further pertains to the use of these crystalline forms in the treatment of cancers and other proliferating diseases and pharmaceutical formulations containing them.

Detailed Description of the Invention

In accordance with the present invention, there are provided polymorphs of an epothilone analog represented by formula I below



I

The epothilone analog represented by formula I chemically is [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione. This analog and the preparation thereof

are described in U.S. patent application Serial No. 09/170,582, filed October 13, 1998, the disclosure of which is incorporated herein by reference. The polymorphs of the analog represented by formula I above are microtubule-stabilizing agents. They are thus useful in the treatment of a variety of cancers and other proliferative diseases including, but not limited to, the following;

- carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin, including squamous cell carcinoma;
- hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burketts lymphoma;
- hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;
- tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;
- other tumors, including melanoma, seminoma, teratocarcinoma, neuroblastoma and glioma;
- tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas;
- tumors of mesenchymal origin, including fibrosarcoma, rhabdomyosarcoma, and osteosarcoma; and
- other tumors, including melanoma, xeroderma pigmentosum, keratoacanthoma, seminoma, thyroid follicular cancer and teratocarcinoma.

The subject polymorphs will also inhibit angiogenesis, thereby affecting the growth of tumors and providing treatment of tumors and tumor-related disorders. Such anti-angiogenesis properties will also be useful in the treatment of other conditions responsive to anti-angiogenesis agents including, but not limited to, certain forms of blindness related to retinal vascularization, arthritis, especially inflammatory arthritis, multiple sclerosis, restinosis and psoriasis.

The polymorphs of the analog represented by formula I will induce or inhibit apoptosis, a physiological cell death process critical for normal development and

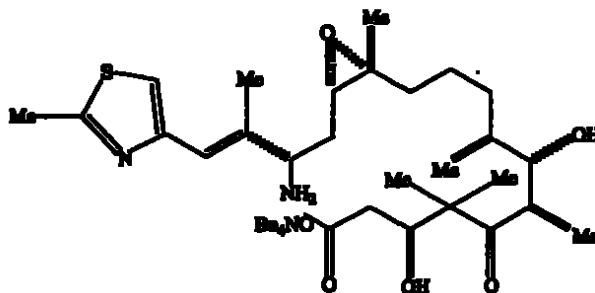
homeostasis. Alterations of apoptotic pathways contribute to the pathogenesis of a variety of human diseases. The subject polymorphs, as modulators of apoptosis, will be useful in the treatment of a variety of human diseases with aberrations in apoptosis including, but not limited to, cancer and precancerous lesions, immune response
5 related diseases, viral infections, degenerative diseases of the musculoskeletal system and kidney disease.

Without wishing to be bound to any mechanism or morphology, the such crystalline forms of the epothilone analog represented by formula I may also be used to treat conditions other than cancer or other proliferative diseases. Such conditions
10 include, but are not limited to viral infections such as herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus; autoimmune diseases such as systemic lupus erythematosus, immune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel diseases and autoimmune diabetes mellitus; neurodegenerative disorders such as Alzheimer's disease, AIDS-related dementia, Parkinson's disease,
15 amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration; AIDS; myelodysplastic syndromes; aplastic anemia; ischemic injury associated myocardial infarctions; stroke and reperfusion injury; restenosis; arrhythmia; atherosclerosis; toxin-induced or alcohol induced liver diseases; hematological diseases such as chronic anemia and aplastic anemia;
20 degenerative diseases of the musculoskeletal system such as osteoporosis and arthritis; aspirin-sensitive rhinosinusitis; cystic fibrosis; multiple sclerosis; kidney diseases; and cancer pain.

The effective amount of the subject polymorphs, particularly Form A, may be determined by one of ordinary skill in the art, and includes exemplary dosage
25 amounts for a human of from about 0.05 to 200 mg/kg/day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. Preferably, the subject polymorphs are administered in a dosage of less than 100 mg/kg/day, in a single dose or in 2 to 4 divided doses. It will be understood that the specific dose level and frequency of dosage for any particular
30 subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the

subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. The subject polymorphs are preferably administered parenterally, however, other routes of administration are contemplated herein as are recognized by those skill in the oncology arts. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like, subject to the aforementioned disorders.

The preparation of the epothilone analogs represented by formula I described in U.S. patent application Serial No. 09/170,582 produced the subject epothilone analog as an oil that can be chromatographed and purified to yield an amorphous powder. A preferred preparation is described in a continuing application under Serial No. 09/528,526 filed on March 20, 2000, the disclosure of which is incorporated herein by reference. In this preparation, as pertains to the analogs represented by formula I, epothilone B is reacted with an azide donor agent and a buffering agent in the presence of a palladium catalyst and a reducing agent to form an intermediate represented by the formula



A macrolactamization reaction is then carried out on the intermediate to form the analog represented by formula I. It has now been found that this analog, in its crystalline form, consists of a mixture of Forms A and B as fully described herein. The amorphous form of the epothilone analog represented by formula I can be taken up in a suitable solvent, preferably a mixed solvent such as ethyl acetate/dichloromethane/triethylamine, purified such as by silica gel pad filtration, and crystallized by cooling to a temperature of about 5°C to form a crystalline material that is a mixture of Form A and Form B. The purification step using a solvent mixture containing a component such as dichloromethane removes residual solvents from the synthesis that could interfere with the crystallization process.

Generally, taking the purified material in a limited amount of ethyl acetate and

heating the resultant slurry to about 75-80°C will cause the formation of Form A. By limited amount is meant from about 8 to 16 mL, preferably from about 8 to 12 mL, of ethyl acetate per gram of purified material. As the solution is heated, a thin slurry forms which has been found to be predominately Form B. At about 75°C the slurry undergoes a material thickening which has been found to be the formation of Form A. The slurry is held at about 75-80°C for about an hour to assure completion of the formation of Form A at which time cyclohexane is added to the slurry in a ratio to ethyl acetate of from about 1:2 to 2:2, preferably about 1:2, and the mixture is allowed to cool to ambient temperature at which it is maintained with stirring for a period of from about 12 to 96 hours. The mixture is then cooled to about 5°C over about two hours after which the crystals of Form A of the subject epothilone analog are recovered. Form A is afforded in good yield and purity.

Alternate procedures for the preparation of Form A involve the addition of seed crystals. In the descriptions that follow, seed crystals of Form A were used, but seed crystals of Form B, or mixtures thereof can be used as well. In one such procedure, the purified material is taken up in a limited amount of ethyl acetate as described above and heated to about 75°C, seed crystals are added and the mixture maintained for about 30 minutes. An amount of cyclohexane as described above is then added dropwise maintaining the temperature at about 70°C. The mixture is thereafter cooled to 20°C and held with stirring for 18 hours after which it is cooled to 5°C and the white crystals of Form A recovered by physical separation, e.g. filtration.

In a second procedure, the initial solution of material in ethyl acetate is heated to 75°C for at least an hour until a solution is produced. The solution is cooled to about 50°C over the course of about two hours adding seed crystals of Form A when the temperature reaches about 60°C. Crystals begin to appear at about 55°C. The temperature is again reduced to about 20°C over a further two hours during one hour of which an amount of cyclohexane as described above is added dropwise. The final slurry is further cooled over two hours to -10°C and held at that temperature for an additional hour. The slurry is then filtered to afford white crystals of Form A.

In a further alternate procedure, the material is taken up in a larger amount, i.e. at least about 40 mL/g of ethyl acetate and the resultant slurry heated to about 80 °C until a solution is formed which is then cooled to about 70°C over the course of about

one hour. Seed crystals of Form A are added when the solution temperature reaches about 70°C. The temperature is then reduced to about 30°C over a further three hours. Crystals begin to appear at about 65°C. The temperature is reduced to -10°C over an additional three hours during a thirty minute period thereof a quantity of
5 cyclohexane as described above is added dropwise. The temperature is maintained at -10°C for a further hour. The final slurry is filtered to afford white crystals of Form A. The yield and purity of Form A by these procedures is considered very good.

Form B of the subject epothilone analogs represented by Formula I above is obtained by forming a slurry of the crude material in a larger quantity of ethyl acetate,
10 i.e. from about 40 to 50 mL per g., and heating at 70°C to 80°C for an hour to form a solution which is then held at temperature for about thirty minutes. The solution is cooled to about 30°C over the course of about two hours, crystals beginning to appear at about 38°C. The temperature is further reduced to about -10°C over one hour during which a quantity of cyclohexane as described above is added dropwise over a
15 period of thirty minutes. The final slurry is held at -10°C over a further two hours and filtered to afford white crystals of Form B.

In an alternative preparation to that above, the crude material is slurried with a like quantity of ethyl acetate and heated to about 78°C to form a solution that is then held at temperature for about thirty minutes. The solution is cooled to about 10°C
20 over the course of about two hours and seed crystals of Form A are added when the temperature reaches about 10°C. The temperature is again reduced over a further two hours to -10°C during a thirty minute period thereof an amount of cyclohexane as described above is added dropwise. The temperature is maintained at -10°C for two hours. The final slurry is filtered to afford white crystals of Form B.

25 In a further alternate procedure, the purified material is taken up in another solvent, preferably toluene, in an amount between about 10 and 20 mL per g., and heated to 75°C to 80°C for 30 minutes and then allowed to cool to 20°C and maintained for 18 hours with stirring. White crystals of Form B are recovered from the slurry by physical separation. The yield and purity of Form B by these procedures
30 is considered very good.

FIGs 1 through 3 are powder x-ray diffraction patterns of Forms A, B and a mixture thereof, respectively, of the subject analog. FIG. 4 is a comparison of powder

x-ray diffraction patterns simulated from the single crystal structures for Forms A and B with the actual pattern for each. X-ray diffraction patterns were generated from a Philips Xpert with a generator source of 44kV and 40 mA and a CuK α filament of $\lambda=1.5406 \text{ \AA}$ at room temperature. In the results shown in FIGs 1-4, as well as in Tables 1 and 2 below which contain the data in summary form, the differences clearly establish that Forms A and B of the subject epothilone analog possess different crystalline structures. In the Tables, Peak Intensities of from 1 to 12 are classified as very weak, from 13 to 32 as weak, from 33 to 64 as average, from 65 to 87 as strong and from 88 to 100 as very strong.

10

Table 1
Values for Form A

Peak Position (two theta) (CuK α $\lambda=1.5406 \text{ \AA}$ at room temperature)	Relative Peak Intensity	Peak Position (two theta)	Relative Peak Intensity
5.69	Very weak	21.06	Very strong
6.76	Very weak	21.29	Weak
8.38	Very weak	22.31	Weak
11.43	Weak	23.02	Weak
12.74	Very weak	23.66	Weak
13.62	Very weak	24.18	Very weak
14.35	Very weak	24.98	Weak
15.09	Very weak	25.50	Weak
15.66	Weak	26.23	Very weak
16.43	Very weak	26.46	Very weak
17.16	Very weak	27.59	Very weak
17.66	Very weak	28.89	Very weak
18.31	Weak	29.58	Very weak
19.03	Weak	30.32	Very weak
19.54	Average	31.08	Very weak
20.57	Weak	31.52	Very weak

Table 2
Values for Form B

Peak Position (two theta) (CuKα λ=1.5406 Å at room temperature)	Relative Peak Intensity	Peak Position (two theta)	Relative Peak Intensity
6.17	Very weak	21.73	Average
10.72	Very weak	22.48	Very strong
12.33	Weak	23.34	Average
14.17	Weak	23.93	Average
14.93	Average	24.78	Average
15.88	Average	25.15	Weak
16.17	Average	25.90	Weak
17.11	Average	26.63	Average
17.98	Weak	27.59	Very weak
19.01	Very strong	28.66	Weak
19.61	Average	29.55	Weak
20.38	Average	30.49	Weak
21.55	Average	31.22	Weak

FIGs 5 through 7 are the results of Raman spectroscopy of Forms A, B and a mixture thereof, respectively, of the subject analog. The spectra also demonstrate two distinct crystal forms, in particular the bands at 3130 cm⁻¹ and 3115 cm⁻¹.

Distinguishing physical characteristics of the two polymorph forms are shown in Table 3 below. Solution calorimetry was determined using a Thermometrics Microcalorimeter in ethanol at 25°C. The solubilities were likewise determined at 25°C. It is further evident from certain of the data, particularly the heat of solution, that Form A is the more stable and, therefore, Form A is preferred.

Table 3

Characteristic	Form A	Form B
Solubility in Water	0.1254	0.1907
Solubility in 3% Polysorbate 80 (Aqueous)	0.2511	0.5799

Heat of Solution	20.6 kJ/mol	9.86 kJ/mol
------------------	-------------	-------------

Form A and Form B of the epothilone analogs represented by formula I above can be further characterized by unit cell parameters obtained from single crystal X-ray crystallographic analysis as set forth below. A detailed account of unit cells can be found in Chapter 3 of Stout & Jensen, X-Ray structure Determination: A Practical Guide, MacMillian Co., New York, NY (1968).

Unit Cell Parameters of Form A

Cell dimensions	a = 14.152(6) Å
	b = 30.72(2) Å
	c = 6.212(3) Å
	Volume = 2701(4) Å ³
Space group	P2 ₁ 2 ₁ 2 ₁
	Orthorhombic
Molecules/unit cell	4
Density (calculated) (g/cm ³)	1.247
Melting point	182-185° C (decomposition)

Unit Cell Parameters of Form B

Cell dimensions	a = 16.675 (2) Å
	b = 28.083(4) Å
	c = 6.054(1) Å
	Volume = 2835(1) Å ³
Space group	P2 ₁ 2 ₁ 2 ₁
	Orthorhombic
Molecules/unit cell	4
Density (calculated) (g/cm ³)	1.187
Melting point	191-199° C (decomposition)

The differences between Forms A and B of the subject epothilone analog are further illustrated by the solid state conformations of each as illustrated in FIG. 8 and FIG. 9, respectively, based on the fractional atomic coordinates listed in Tables 4 through 7 below.

Table 4

Fractional Atomic Coordinates for the Epothilone Analog of Formula I: Form A

Atom	X	Y	Z	U11*10e2
C1	0.3879(3)	0.4352(1)	0.5503(9)	60(6)

	O1	0.4055(2)	0.4300(1)	0.7435(5)	68(4)
	C2	0.2864(3)	0.4340(1)	0.4675(7)	42(6)
	C3	0.2696(3)	0.4210(1)	0.2325(7)	56(6)
	O3	0.3097(2)	0.4550(1)	0.1027(5)	71(4)
5	C4	0.1615(3)	0.4154(1)	0.1852(7)	50(6)
	C5	0.1289(3)	0.3732(1)	0.2895(8)	58(6)
	O5	0.0935(3)	0.3748(1)	0.4713(6)	135(6)
	C6	0.1343(3)	0.3296(1)	0.1769(8)	66(6)
	C7	0.1503(3)	0.2921(1)	0.3353(8)	84(6)
10	O7	0.1410(3)	0.2528(1)	0.2127(6)	127(5)
	C8	0.2449(4)	0.2936(1)	0.4540(8)	83(7)
	C9	0.3284(4)	0.2824(1)	0.3072(9)	81(7)
	C10	0.4258(4)	0.2877(1)	0.4141(8)	76(7)
	C11	0.4467(3)	0.3359(1)	0.4622(8)	67(6)
15	C12	0.5220(3)	0.3426(1)	0.6294(8)	53(6)
	O12	0.6171(2)	0.3288(1)	0.5612(5)	56(4)
	C13	0.5983(3)	0.3746(1)	0.5991(8)	50(6)
	C14	0.6099(3)	0.4053(1)	0.4113(8)	47(6)
	C15	0.5568(3)	0.4477(1)	0.4538(8)	44(6)
20	N16	0.4552(3)	0.4426(1)	0.4005(6)	41(5)
	C17	0.1482(4)	0.4138(2)	-0.0603(8)	103(7)
	C18	0.1043(4)	0.4539(1)	0.2734(8)	62(6)
	C19	0.0386(4)	0.3232(2)	0.0572(10)	92(8)
	C20	0.2404(5)	0.2630(2)	0.6482(10)	145(9)
25	C21	0.4974(4)	0.3301(2)	0.8563(9)	109(8)
	C22	0.5935(3)	0.4860(1)	0.3281(8)	48(6)
	C23	0.5989(4)	0.4815(2)	0.0875(8)	132(8)
	C24	0.6154(3)	0.5222(1)	0.4376(8)	59(6)
	C25	0.6392(3)	0.5656(1)	0.3573(8)	61(6)
30	N26	0.6786(3)	0.5941(1)	0.5076(6)	75(6)
	C27	0.6902(3)	0.6325(2)	0.4255(8)	59(6)
	S28	0.6529(1)	0.6381(1)	0.1655(2)	92(2)
	C29	0.6196(4)	0.5846(2)	0.1632(9)	85(7)
	C30	0.7292(4)	0.6703(2)	0.5523(10)	106(8)

35 Table 4 Continued

	U22*10e2	U33*10e2	U12*10e2	U13*10e2	U23*10e2
	25(4)	138(8)	-2(4)	16(5)	-9(4)
	85(4)	100(5)	6(3)	4(3)	1(3)
	64(5)	106(6)	0(4)	3(4)	-5(4)
40	44(5)	103(6)	-7(4)	5(4)	13(4)
	58(3)	128(4)	-6(3)	18(3)	3(3)
	63(5)	112(6)	-12(4)	-3(4)	7(4)
	82(6)	103(7)	-6(4)	-13(5)	4(5)
	83(4)	144(5)	-16(4)	39(4)	5(3)
45	71(5)	118(6)	-13(5)	-7(4)	-10(4)
	43(5)	134(6)	-27(4)	-2(5)	-10(5)
	61(4)	163(5)	-34(3)	-17(4)	-9(3)

	56(5)	127(6)	-26(5)	-4(5)	3(5)
	68(5)	153(7)	-1(5)	-4(5)	-26(5)
	56(5)	166(8)	13(5)	-19(5)	-15(5)
	61(5)	126(7)	-3(4)	-19(4)	-5(5)
5	64(5)	138(7)	16(4)	8(5)	-1(5)
	61(3)	155(4)	15(3)	8(3)	4(3)
	45(5)	162(7)	3(4)	2(5)	-8(5)
	63(5)	159(7)	2(4)	5(5)	7(5)
	44(5)	143(6)	-4(4)	7(4)	-1(4)
10	65(4)	106(5)	-3(3)	6(3)	-2(3)
	128(7)	104(7)	-29(6)	-10(5)	18(5)
	67(5)	164(7)	17(5)	9(5)	12(5)
	115(7)	217(10)	-17(6)	-70(7)	-19(7)
	114(7)	158(8)	-34(6)	-20(6)	47(6)
15	92(6)	131(7)	19(5)	10(5)	8(5)
	63(5)	122(6)	6(4)	4(5)	-1(5)
	78(6)	116(7)	-7(5)	12(5)	-13(5)
	55(5)	132(6)	-6(4)	9(5)	7(5)
	65(5)	127(7)	-12(4)	8(5)	5(5)
20	58(5)	129(5)	-9(4)	4(4)	-5(4)
	69(6)	128(6)	9(4)	2(5)	7(5)
	79(1)	163(2)	-10(1)	-3(1)	20(1)
	78(6)	161(8)	-13(5)	-9(6)	3(6)
	75(6)	186(8)	-29(5)	-5(6)	-10(6)
25					

Table 5

Hydrogen Positions: Form A

	Atom	X	Y	Z	U*10E2
5	H21	0.2475(0)	0.4114(0)	0.5659(0)	4.86(0)
	H22	0.2576(0)	0.4663(0)	0.4871(0)	4.86(0)
	H31	0.3056(0)	0.3905(0)	0.2005(0)	4.59(0)
	H3	0.3433(0)	0.4414(0)	-0.0241(0)	5.55(0)
	H61	0.1951(0)	0.3304(0)	0.0646(0)	5.55(0)
10	H71	0.0960(0)	0.2932(0)	0.4607(0)	5.80(0)
	H7	0.1332(0)	0.2276(0)	0.3158(0)	7.23(0)
	H81	0.2588(0)	0.3266(0)	0.5107(0)	5.85(0)
	H91	0.3274(0)	0.3037(0)	0.1672(0)	6.41(0)
	H92	0.3217(0)	0.2491(0)	0.2527(0)	6.41(0)
15	H101	0.4802(0)	0.2743(0)	0.3130(0)	6.34(0)
	H102	0.4253(0)	0.2697(0)	0.5663(0)	6.34(0)
	H111	0.4687(0)	0.3519(0)	0.3132(0)	5.60(0)
	H112	0.3823(0)	0.3519(0)	0.5172(0)	5.60(0)
	H131	0.6275(0)	0.3905(0)	0.7410(0)	5.60(0)
20	H141	0.6837(0)	0.4117(0)	0.3814(0)	5.88(0)
	H142	0.5803(0)	0.3901(0)	0.2659(0)	5.88(0)
	H151	0.5638(0)	0.4542(0)	0.6281(0)	5.35(0)
	H16	0.4353(0)	0.4447(0)	0.2429(0)	4.88(0)
	H171	0.1722(0)	0.4437(0)	-0.1367(0)	6.90(0)
25	H172	0.1919(0)	0.3871(0)	-0.1308(0)	6.90(0)
	H173	0.0763(0)	0.4077(0)	-0.1076(0)	6.90(0)
	H181	0.1273(0)	0.4835(0)	0.1956(0)	6.31(0)
	H182	0.0295(0)	0.4491(0)	0.2355(0)	6.31(0)
	H183	0.1123(0)	0.4566(0)	0.4436(0)	6.31(0)
30	H191	0.0370(0)	0.2923(0)	-0.0226(0)	8.78(0)
	H192	-0.0186(0)	0.3233(0)	0.1794(0)	8.78(0)
	H193	0.0259(0)	0.3491(0)	-0.0525(0)	8.78(0)
	H201	0.3050(0)	0.2635(0)	0.7355(0)	8.17(0)
	H202	0.1828(0)	0.2733(0)	0.7536(0)	8.17(0)
35	H203	0.2252(0)	0.2304(0)	0.5923(0)	8.17(0)
	H211	0.4260(0)	0.3415(0)	0.8951(0)	6.84(0)
	H212	0.4998(0)	0.2955(0)	0.8754(0)	6.84(0)

Table 6

40 Fractional Atomic Coordinates for the Epothilone Analog of Formula I: Form B

	Atom	X	Y	Z	U11*10e2
45	C1	0.2316(2)	0.1043(2)	0.7342(8)	56(4)
	O1	0.2321(2)	0.1159(1)	0.5376(5)	131(4)
	C2	0.1812(2)	0.0623(1)	0.8106(7)	62(4)
	C3	0.1535(2)	0.0622(1)	1.0506(7)	52(4)
	O3	0.2226(2)	0.0539(1)	1.1856(5)	65(3)
	C4	0.0876(2)	0.0237(1)	1.0903(7)	63(4)
	C5	0.0096(2)	0.0415(1)	0.9838(8)	57(4)

	O5	-0.0132(2)	0.0252(1)	0.8117(6)	100(4)
	C6	-0.0409(2)	0.0796(1)	1.1023(6)	53(4)
	C7	-0.0754(2)	0.1151(1)	0.9373(9)	60(4)
	O7	-0.1316(2)	0.1434(1)	1.0606(7)	79(3)
5	C8	-0.0135(3)	0.1468(1)	0.8213(8)	75(5)
	C9	0.0274(2)	0.1817(1)	0.9812(9)	80(5)
	C10	0.0946(3)	0.2107(2)	0.8766(10)	95(5)
	C11	0.1389(3)	0.2407(2)	1.0447(11)	97(5)
	C12	0.2065(3)	0.2688(2)	0.9440(11)	110(6)
10	O12	0.2653(2)	0.2862(1)	1.1070(8)	124(4)
	C13	0.2894(3)	0.2520(2)	0.9406(10)	104(6)
	C14	0.3190(3)	0.2049(2)	1.0281(10)	117(6)
	C15	0.3253(3)	0.1676(1)	0.8388(8)	86(5)
	N16	0.2738(2)	0.1273(1)	0.8901(7)	64(4)
15	C17	0.0762(3)	0.0176(2)	1.3416(8)	102(6)
	C18	0.1109(2)	-0.0244(1)	0.9909(8)	82(5)
	C19	-0.1098(3)	0.0529(2)	1.2197(10)	79(5)
	C20	-0.0528(3)	0.1729(2)	0.6272(9)	149(7)
	C21	0.1829(4)	0.3056(2)	0.7748(15)	175(9)
20	C22	0.4128(3)	0.1527(2)	0.7991(8)	80(5)
	C23	0.4521(4)	0.1784(3)	0.6109(13)	141(8)
	C24	0.4477(3)	0.1216(2)	0.9319(9)	88(5)
	C25	0.5303(3)	0.1032(2)	0.9346(9)	76(5)
	N26	0.5822(2)	0.1091(2)	0.7577(8)	71(5)
25	C27	0.6498(3)	0.0890(2)	0.7986(10)	98(6)
	S28	0.6565(1)	0.0612(1)	1.0487(3)	107(1)
	C29	0.5605(3)	0.0785(2)	1.1053(10)	93(6)
	C30	0.7206(4)	0.0891(3)	0.6410(12)	102(7)

30 Table 6 Continued

	U22*10e2	U33*10e2	U12*10e2	U13*10e2	U23*10e2
	74(5)	86(6)	5(4)	-6(4)	-16(5)
	88(3)	74(4)	-24(3)	-13(3)	-7(3)
	85(5)	68(5)	-7(4)	-6(4)	-22(5)
35	67(4)	71(5)	1(3)	-19(4)	-6(4)
	123(4)	96(4)	7(3)	-29(3)	-19(4)
	75(4)	63(5)	5(4)	-4(4)	-10(4)
	61(4)	78(5)	-7(3)	-2(4)	-10(4)
	103(4)	100(4)	19(3)	-38(3)	-38(4)
40	77(4)	92(6)	14(4)	2(5)	-17(5)
	111(4)	185(5)	40(3)	22(4)	-10(4)
	74(5)	106(6)	4(4)	8(5)	-14(5)
	69(4)	136(7)	-10(4)	-1(5)	-19(5)
	89(5)	175(8)	-21(4)	15(7)	-27(6)
45	98(6)	191(9)	-22(5)	27(7)	-48(7)
	64(5)	208(9)	-16(5)	10(7)	-28(6)
	98(4)	241(7)	-36(3)	30(5)	-77(5)
	82(5)	169(9)	-25(5)	23(6)	-38(6)

	102(6)	160(8)	-3(5)	-26(6)	-53(6)
	74(5)	107(6)	-18(4)	-17(5)	-15(5)
	100(4)	98(5)	-26(3)	-13(4)	-19(4)
	129(6)	66(5)	-13(5)	-5(5)	10(5)
5	58(4)	113(6)	13(4)	-11(5)	-9(5)
	139(7)	187(9)	1(5)	54(6)	29(7)
	116(6)	123(8)	10(6)	-19(6)	22(6)
	86(6)	338(15)	-8(6)	0(11)	21(9)
	80(5)	108(6)	-29(4)	-5(5)	-6(5)
10	261(11)	237(13)	28(8)	54(9)	146(11)
	111(6)	111(7)	-5(5)	3(5)	21(6)
	96(5)	119(7)	-12(4)	2(5)	-2(6)
	192(7)	114(6)	2(5)	-6(5)	3(6)
	165(7)	125(7)	-5(6)	-13(6)	-19(7)
15	128(2)	173(2)	12(1)	-25(2)	0(2)
	122(6)	166(9)	4(5)	3(6)	43(7)
	443(17)	150(10)	45(10)	18(7)	-17(12)

Table 7

20 Hydrogen Positions: Form B

	Atom	X	Y	Z	U*10E2
	H21	0.1283(0)	0.0616(0)	0.7084(0)	4.86(0)
	H22	0.2159(0)	0.0306(0)	0.7857(0)	4.86(0)
	H31	0.1272(0)	0.0969(0)	1.0910(0)	4.51(0)
25	H3	0.2243(0)	0.0785(0)	1.3075(0)	6.11(0)
	H61	-0.0043(0)	0.0983(0)	1.2199(0)	4.99(0)
	H71	-0.1059(0)	0.0964(0)	0.8057(0)	5.69(0)
	H7	-0.1609(0)	0.1655(0)	0.9542(0)	7.62(0)
	H81	0.0313(0)	0.1244(0)	0.7484(0)	5.58(0)
30	H91	-0.0180(0)	0.2062(0)	1.0453(0)	6.10(0)
	H92	0.0520(0)	0.1619(0)	1.1189(0)	6.10(0)
	H101	0.1365(0)	0.1874(0)	0.7953(0)	7.47(0)
	H102	0.0691(0)	0.2349(0)	0.7527(0)	7.47(0)
	H111	0.0976(0)	0.2651(0)	1.1204(0)	7.74(0)
35	H112	0.1633(0)	0.2170(0)	1.1686(0)	7.74(0)
	H131	0.3308(0)	0.2613(0)	0.8107(0)	7.31(0)
	H141	0.3779(0)	0.2094(0)	1.1016(0)	7.61(0)
	H142	0.2780(0)	0.1920(0)	1.1530(0)	7.61(0)
	H151	0.3046(0)	0.1836(0)	0.6859(0)	5.74(0)
40	H16	0.2693(0)	0.1161(0)	1.0487(0)	5.71(0)
	H171	0.0304(0)	-0.0088(0)	1.3753(0)	6.33(0)
	H172	0.1318(0)	0.0064(0)	1.4171(0)	6.33(0)
	H173	0.0577(0)	0.0512(0)	1.4165(0)	6.33(0)
	H181	0.0633(0)	-0.0501(0)	1.0184(0)	5.58(0)
45	H182	0.1192(0)	-0.0207(0)	0.8122(0)	5.58(0)
	H183	0.1655(0)	-0.0370(0)	1.0628(0)	5.58(0)
	H191	-0.1481(0)	0.0774(0)	1.3099(0)	8.04(0)
	H192	-0.1459(0)	0.0330(0)	1.1036(0)	8.04(0)

	H193	-0.0849(0)	0.0274(0)	1.3402(0)	8.04(0)
	H201	-0.0094(0)	0.1955(0)	0.5429(0)	7.89(0)
	H202	-0.0763(0)	0.1475(0)	0.5059(0)	7.89(0)
	H203	-0.1024(0)	0.1951(0)	0.6816(0)	7.89(0)
5	H211	0.1596(0)	0.2886(0)	0.6259(0)	11.47(0)
	H212	0.1382(0)	0.3292(0)	0.8404(0)	11.47(0)
	H213	0.2355(0)	0.3265(0)	0.7267(0)	11.47(0)
	H231	0.5051(0)	0.1602(0)	1.0559(0)	6.57(0)
	H291	0.5291(0)	0.0702(0)	1.2584(0)	7.73(0)
10	H301	0.7003(0)	0.0920(0)	0.4744(0)	13.05(0)
	H302	0.7623(0)	0.1165(0)	0.6811(0)	13.05(0)
	H303	0.7525(0)	0.0542(0)	0.6572(0)	13.05(0)

15 Based on the foregoing data, it is concluded that Forms A and B are unique crystalline entities.

The following non-limiting examples serve to illustrate the practice of the invention.

20

Example 1

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione.

25

To a jacketed 125 mL round bottom flask, fitted with a mechanical stirrer, there was combined epothilone-B (5.08 g), tetrabutylammonium azide (Bu_4NN_3) (3.55 g, 1.25 equivalents), ammonium chloride (1.07g, 2 eq), water (1.8 ml, 10 equivalents), tetrahydrofuran (THF) (15 ml), and N,N-dimethylformamide (DMF) (15 ml). The mixture was inerted by sparging nitrogen subsurface for 15 minutes. In a second flask was charged tetrahydrofuran (70 ml), followed by trimethylphosphine (PMe_3) (1.56 ml, 1.5 equivalents), then tris(dibenzilideneacetone)-dipalladium(0)-chloroform adduct ($\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$) (0.259 g, 0.025 equivalents). The catalyst mixture was stirred for 20 minutes at ambient temperature, then added to the epothilone-B mixture. The combined mixture was stirred for 4.5 hours at 30 °C. The completed reaction mixture was then filtered to remove solid ammonium chloride (NH_4Cl). The filtrate contained (βS , ϵR , ζS , ηS , 2R, 3S)-3-[(2S, 3E)-2-amino-3-

35

methyl-4-(2-methyl-4-thiazolyl)-3-butenyl]- β , ζ -dihydroxy- γ , γ , ϵ , η , 2-pentamethyl- δ -oxooxiraneundecanoic acid, tetrabutylammonium salt (1:1) with a HPLC area of 94.1%.

In a 500 mL flask there was combined 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) (3.82 g, 2 equivalents), 1-hydroxy-7-benzotriazole hydrate (HOBt) (1.68 g, 1.1 equivalents), potassium carbonate (1.38 g, 1 equivalent), N, N-dimethylformamide (DMF) (40 ml) and tetrahydrofuran (THF) (160 ml). The mixture was warmed to 35°C and the filtrate from above was added thereto, dropwise over a period of three hours. This mixture was then stirred for an additional 1 hour at 35 °C. Vacuum distillation was then applied to the reaction mixture to reduce the volume thereof to about 80 mL. The resulting solution was partitioned between 100 mL of ethyl acetate and 100 mL of water. The aqueous layer was then back-extracted with 100 ml ethyl acetate. The combined organic layers were extracted with 50 ml water and then 20 mL brine. The resulting product solution was filtered through a Zeta Plus® pad and then stripped to an oil. The crude oil was dissolved in dichloromethane (20 mL) and washed with water to remove final traces of synthesis solvents and stripped to a solid. The crude solid was chromatographed on silica gel 60 (35 ml silica per gram of theoretical product) with an eluent comprised of 88% dichloromethane (CH₂Cl₂), 10%-30% ethyl acetate (EtOAc) and 2% triethylamine (Et₃N). The fractions were analyzed by HPLC, the purest of which were combined and stripped to give the purified solid. The resulting solid, approx. 2 g, was slurried in ethyl acetate (32 ml) for 40 minutes at 75°C, then cyclohexane (C₆H₁₂) (16 ml) was slowly added, and the mixture cooled to 5°C. The purified solid was collected on filter paper, washed with cold ethyl acetate/cyclohexane, and dried. The yield was 1.72 g (38% yield) of the white solid product, [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione, with a HPLC area of 99.2%.

Example 2

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione, Form A.

5

A 250 mL three-neck flask was charged with 0.61 g of the title compound that had been purified (silica gel pad filtration with EtOAc/hexane/Et₃N as the eluent, HPLC area of 96.88) and ethyl acetate (28 mL, 46 ml/1 g). The resultant slurry was heated to 75°C. All of solids were dissolved after the slurry was stirred at 75°C for 10 60 minutes. The afforded solution was cooled from 75°C to 50°C over 120 minutes, seed crystals of Form A being added at 60°C. Crystals appeared at 55°C. The temperature was thereafter cooled to 20°C over 120 minutes, while cyclohexane (35 mL, 57 mL/1 g) was added dropwise to the mixture over a period of 60 minutes. The obtained slurry was cooled to -10°C over 120 minutes, and maintained for an 15 additional 60 minutes. The slurry was filtered and the afforded white crystals were dried to give 0.514 g of the title compound, Form A, in 84.3% yield with an HPLC area of 99.4.

Form A – Alternate Procedure

20 A 250 mL three-neck flask was charged with 0.51 g of the title compound that had been purified (silica gel pad filtration with EtOAc/hexane/Et₃N as the eluent, HPLC area of 96) and ethyl acetate (8.5 mL, 16.7 ml/1 g). The resultant slurry was heated to 80°C. The afforded solution was cooled from 80°C to 70°C over 60 minutes, seed crystals of Form A being added at 70°C. The temperature was 25 thereafter cooled to 30°C over 180 minutes. Crystals appeared at 65°C. The solution was further cooled to -10°C over 180 minutes, while cyclohexane (10.2 mL, 20 mL/1 g) was added dropwise to the mixture over a period of 30 minutes. The obtained slurry was cooled maintained for an additional 60 minutes. The slurry was filtered and the afforded white crystals were dried to give 0.43 g of the title 30 compound, Form A, in 84.3% yield with an HPLC area of 99.7.

Form A – Alternate Procedure

A 500 mL three-neck flask was charged with 18.3 g of a mixture of Forms A and B that had been purified (silica gel pad filtration with EtOAc/dichloromethane/Et₃N as the eluent, HPLC area of 99) and ethyl acetate (183 mL, 10 mL/1 g). The resultant slurry was heated to 75°C, seed crystals of Form A were added and the temperature was maintained for 30 minutes. Cyclohexane (90.2 mL, 5 mL/1 g) was added dropwise to the mixture keeping the temperature at 70°C. After completion of the addition, the temperature was lowered to 20°C and the mixture maintained with stirring for a further 18 hours. The temperature was thereafter lowered to 5°C and maintain for 5 hours. The slurry was filtered and the afforded white crystals were dried to give 16.1 g of the title compound, Form A, in 88% yield with an HPLC area of 99.49.

Example 3

15 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione, Form B.

A 250 mL three-neck flask was charged with 0.108 g of the title compound that had not been purified as in Example 2, N,N-dimethyl formamide (0.0216 g) and ethyl acetate (5 mL, 46 mL/1 g). The resultant slurry was heated to 80°C and stirred for 30 minutes to dissolve all solids. The afforded solution was cooled from 80°C to 30°C over 120 minutes, crystals appearing at 38°C. Cyclohexane (7.5 mL, 69.5 mL/1 g) was added dropwise to the mixture over a period of 30 minutes while the temperature was cooled to -10°C over 60 minutes, and maintained for an additional 120 minutes. The slurry was filtered and the afforded white crystals were dried to give 0.082g of the title compound, Form B, in 76% yield with an HPLC area of 99.6.

Form B – Alternate Procedure

30 A 250 mL three-neck flask was charged with 0.458 g of the title compound that had not been purified as in Example 2 and contained about 6% of N,N-dimethyl formamide and ethyl acetate (10 mL, 21.8 mL/1 g). The resultant slurry was heated to

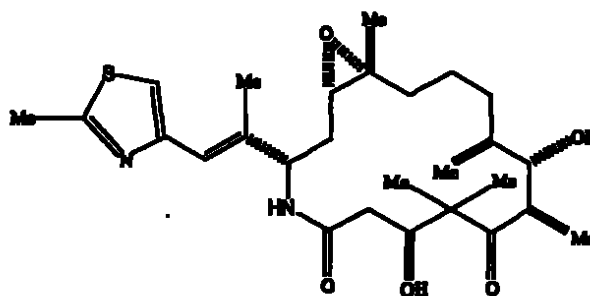
78°C and stirred for 30 minutes to dissolve all solids. The afforded solution was cooled from 78°C to 10°C over 120 minutes. Seed crystals of Form A were added at 10°C. Cyclohexane (20 mL, 43.7 mL/1 g) was added dropwise to the mixture over a period of 60 minutes while the temperature was cooled to -10°C over 120 minutes, and maintained for an additional 120 minutes. The slurry was filtered and the afforded white crystals were dried to give 0.315g of the title compound, Form B, in 68.8% yield with an HPLC area of 98.2.

Form B – Alternate Procedure

10 A 5-mL Wheaton bottle was charged with 250 mg of the title compound that had not been purified as in Example 2 and toluene (3.75 mL, 15 mL/g.) and the resultant slurry heated to 75°C and held for 30 minutes. The resultant suspension was allowed to cool to 20°C and maintained at that temperature for 18 hours with stirring. The slurry was filtered and the afforded white crystals dried to give 150 mg. of the
15 title compound, Form B, in 60% yield with an HPLC area of 99.2

We claim:

1. A crystalline polymorph of an epothilone analog represented by the formula



I

comprising Form A characterized by:

unit cell parameters approximately equal to the following:

10	Cell dimensions	$a = 14.152(6) \text{ \AA}$ $b = 30.72(2) \text{ \AA}$ $c = 6.212(3) \text{ \AA}$ Volume = $2701(4) \text{ \AA}^3$
	Space group	$P2_12_12_1$ Orthorhombic
15	Molecules/unit cell	4
	Density (calculated) (g/cm^3)	1.247
	Melting point	$182\text{--}185^\circ \text{C}$ (decomposition); and

- 20 characteristic peaks in the powder x-ray diffraction pattern at values of two theta ($\text{CuK}\alpha$ $\lambda = 1.5406 \text{ \AA}$ at 22°C): 5.69, 6.76, 8.38, 11.43, 12.74, 13.62, 14.35, 15.09, 15.66, 16.43, 17.16, 17.66, 18.31, 19.03, 19.54, 20.57, 21.06, 21.29, 22.31, 23.02, 23.66, 24.18, 24.98, 25.50, 26.23, 26.23, 26.46, 27.59, 28.89, 29.58, 30.32, 31.08 and 31.52; or

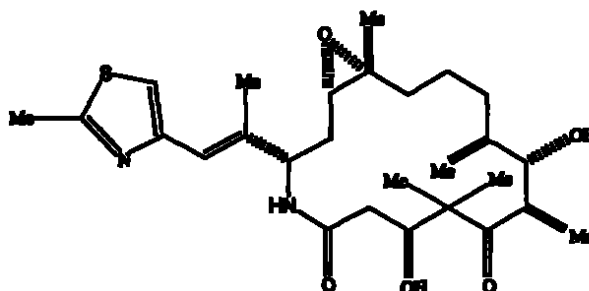
- 25 Form B is characterized by:

unit cell parameters approximately equal to the following:

30	Cell dimensions	$a = 16.675(2) \text{ \AA}$ $b = 28.083(4) \text{ \AA}$ $c = 6.054(1) \text{ \AA}$ Volume = $2835(1) \text{ \AA}^3$
	Space group	$P2_12_12_1$ Orthorhombic
	Molecules/unit cell	4
	Density (calculated) (g/cm^3)	1.187
35	Melting point	$191\text{--}199^\circ \text{C}$ decomposition; and

characteristic peaks in the powder x-ray diffraction pattern at values of two theta ($\text{CuK}\alpha$ $\lambda=1.5406$ Å at 22°C): 6.17, 10.72, 12.33, 14.17, 14.93, 15.88, 16.17, 17.11, 17.98, 19.01, 19.61, 20.38, 21.55, 21.73, 22.48, 23.34, 23.93, 24.78, 25.15, 25.90, 26.63, 27.59, 28.66, 29.55, 30.49 and 31.22.

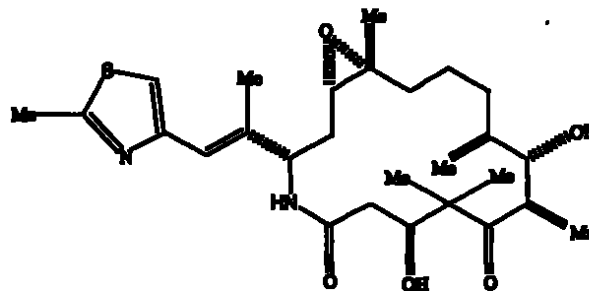
2. A crystalline polymorph of an epothilone analog represented by the formula



I

comprising Form A characterized by powder x-ray diffraction substantially as shown in FIG. 1 and a Raman spectrum substantially as shown in FIG. 5; or Form B characterized by powder x-ray diffraction substantially as shown in FIG. 2 and a Raman spectrum substantially as shown in FIG. 6.

3. A crystalline polymorph of an epothilone analog represented by the formula



I

comprising Form A characterized by a solubility in water of 0.1254, a solubility in a 3% aqueous solution of polysorbate 80 of 0.2511, a melting point with decomposition between 182-185° C and a heat of solution of 20.6 kJ/mol; or Form B characterized by a solubility in water of 0.1907, a solubility in a 3% aqueous solution of polysorbate 80 of 0.5799, a melting point with decomposition between 191-199° C and a heat of solution of 9.86 kJ/mol.

4. A crystalline polymorph in accordance with Claims 1, 2 or 3, wherein said polymorph is Form A.
5. A crystalline polymorph in accordance with Claims 1, 2 or 3, wherein said polymorph is Form B.
6. A crystalline material comprising a mixture of Form A and Form B in accordance with Claim 1, 2 or 3.
7. A process for producing a crystalline polymorph that is Form A of the epothilone analog represented by formula I in Claim 1 comprising heating a slurry of said analog represented by formula I in from about 8 to about 16 mL of ethyl acetate per gram of said analog to about 75°C maintaining the temperature for about one hour, adding an amount of cyclohexane in a ratio to the amount of ethyl acetate of from about 1:2 to about 2:2, allowing the mixture to cool to ambient temperature, maintain the mixture with stirring from about 12 to 96 hours, further cooling it to about 5°C over about two hours and recovering the crystalline Form A therefrom.
8. A process in accordance with Claim 7 wherein the amount of cyclohexane added is in a 1:2 ratio to the amount of ethyl acetate utilized to form said slurry.
9. A process in accordance with Claim 7, wherein said slurry of said analog represented by formula I in ethyl acetate is heated to about 75°C seed crystals are added thereto and the mixture is maintained for about 30 minutes after which said amount of cyclohexane is added thereto while maintaining the mixture at about 70°C, cooling the mixture to ambient temperature, maintain the mixture with stirring for about 18 hours, further cooling it to about 5°C over about two hours and recovering the crystalline Form A therefrom.
10. A process in accordance with Claim 7, wherein said slurry of said analog represented by formula I in ethyl acetate is heated to about 75°C for at least an hour until a solution is formed, cooling said solution to about 50°C over about two hours,

adding said seed crystals thereto when the temperature reaches about 60°C , cooling the solution to about 30°C over about three hours, further reducing the temperature of the solution to -10°C over about three hours during one hour of which said amount of cyclohexane is added thereto dropwise, maintaining the resultant mixture at -10°C for about one hour and recovering the crystalline Form A therefrom.

11. A process for producing a crystalline polymorph that is Form B of the epothilone analog represented by formula I in Claim 1 comprising heating a slurry of said analog represented by formula I in from about 40 to about 50 mL of ethyl acetate per gram of said analog to about 75°C to 80°C, maintaining the temperature for about one hour thereby forming a solution, maintaining the solution at temperature for about 30 minutes, cooling the solution to about 30°C over about two hours, further reducing the temperature of the solution to -10°C over about one hour during which an amount of cyclohexane in a ratio to the amount of ethyl acetate of from about 1:2 to about 2:2 is added thereto dropwise over a period of about thirty minutes, maintaining the resultant mixture at -10°C for about two hours and recovering the crystalline Form B therefrom.

12. A process in accordance with Claim 11, wherein said slurry of said analog represented by formula I in ethyl acetate is heated to about 78°C thereby forming a solution, cooling the solution to about 10°C over about two hours, adding seed crystals when the temperature reaches 10°C, further reducing the temperature of the solution to -10°C over about two hours during which said amount of cyclohexane is added thereto dropwise over a period of about thirty minutes, maintaining the resultant mixture at -10°C for about two hours and recovering the crystalline Form B therefrom.

13. A process for producing a crystalline polymorph that is Form B of the epothilone analog represented by formula I in Claim 1 comprising heating a slurry of said analog represented by formula I in from about 10 to about 20 mL of toluene per gram of said analog to about 75°C to 80°C, maintaining the temperature for about 30

minutes, cooling the mixture to about 20°C, maintaining the temperature for about 18 hours with stirring and recovering the crystalline Form B therefrom.

14. A pharmaceutical composition which comprises as an active ingredient an effective amount a crystalline polymorph as claimed in Claims 1, 2 or 3 and one or more pharmaceutically acceptable carriers, excipients or diluents thereof.

15. A pharmaceutical composition in accordance with Claim 14, wherein said crystalline polymorph is Form A.

10

16. A pharmaceutical composition in accordance with Claim 14, wherein said crystalline polymorph is Form B.

17. A pharmaceutical composition in accordance with Claim 14, wherein said crystalline polymorph is a mixture of Form A and Form B.

15

18. A method for treating cancer or other proliferative diseases which comprises administering to a mammal in need thereof an effective amount of a crystalline polymorph as claimed in Claims 1, 2 or 3.

20

19. A method in accordance with Claim 18, wherein said crystalline polymorph is Form A.

20. A method in accordance with Claim 18, wherein said crystalline polymorph is Form B.

25

21. A method in accordance with Claim 18, wherein said crystalline polymorph is administered parenterally.

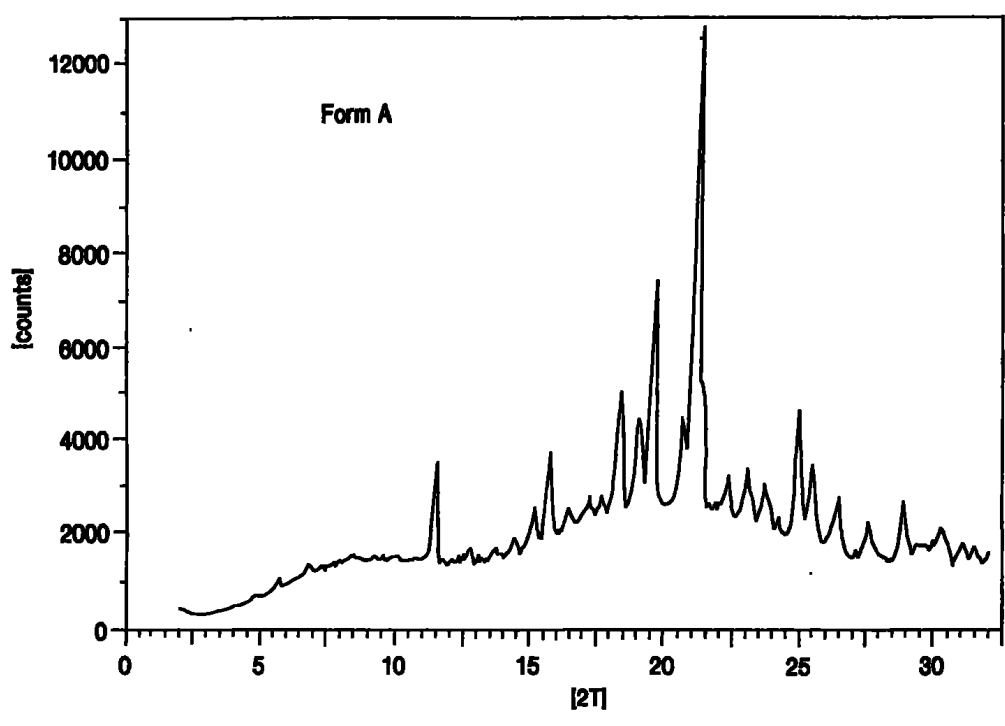


FIG. 1

54

WO 02/14323

2/9

PCT/US01/24540

1154

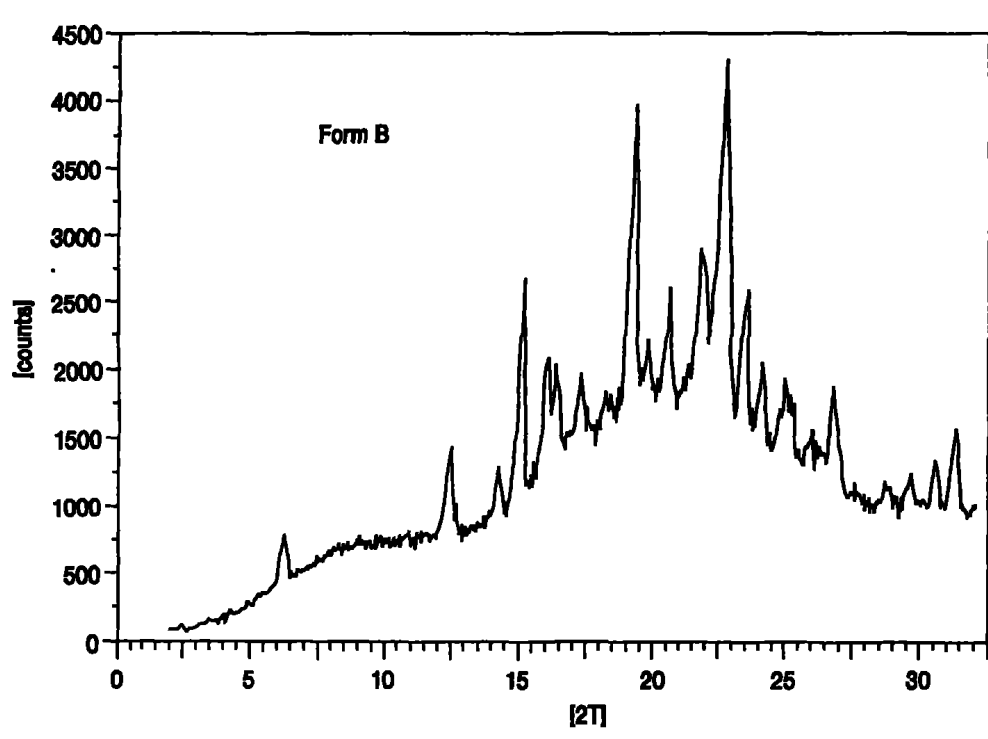


FIG. 2

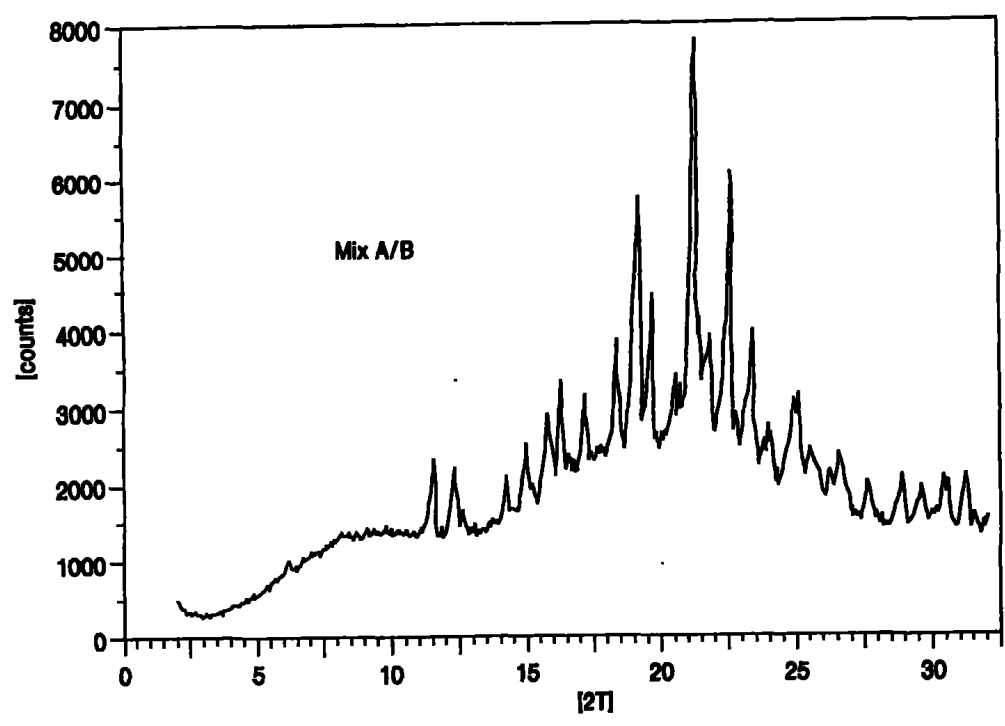


FIG. 3

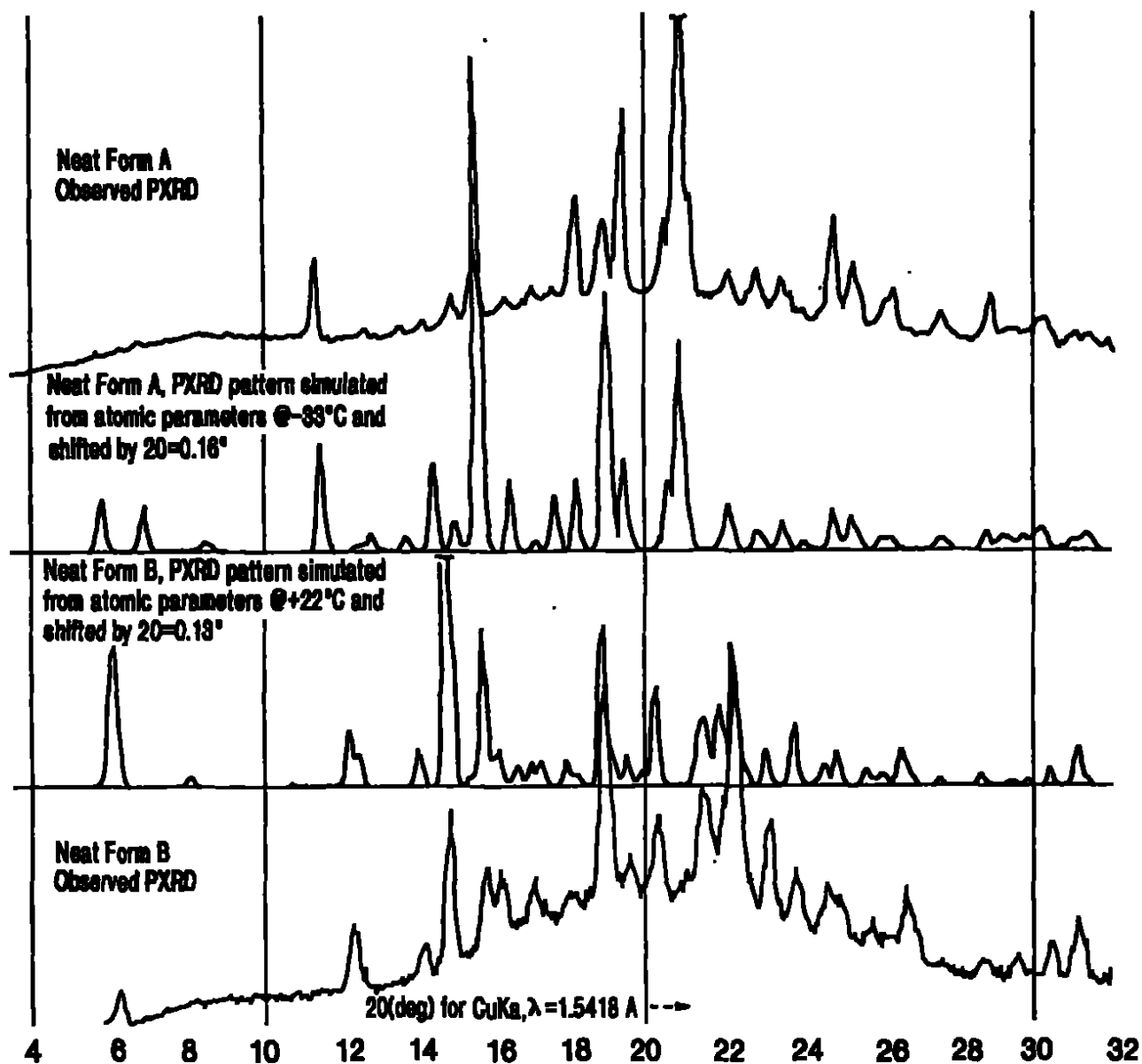


FIG. 4

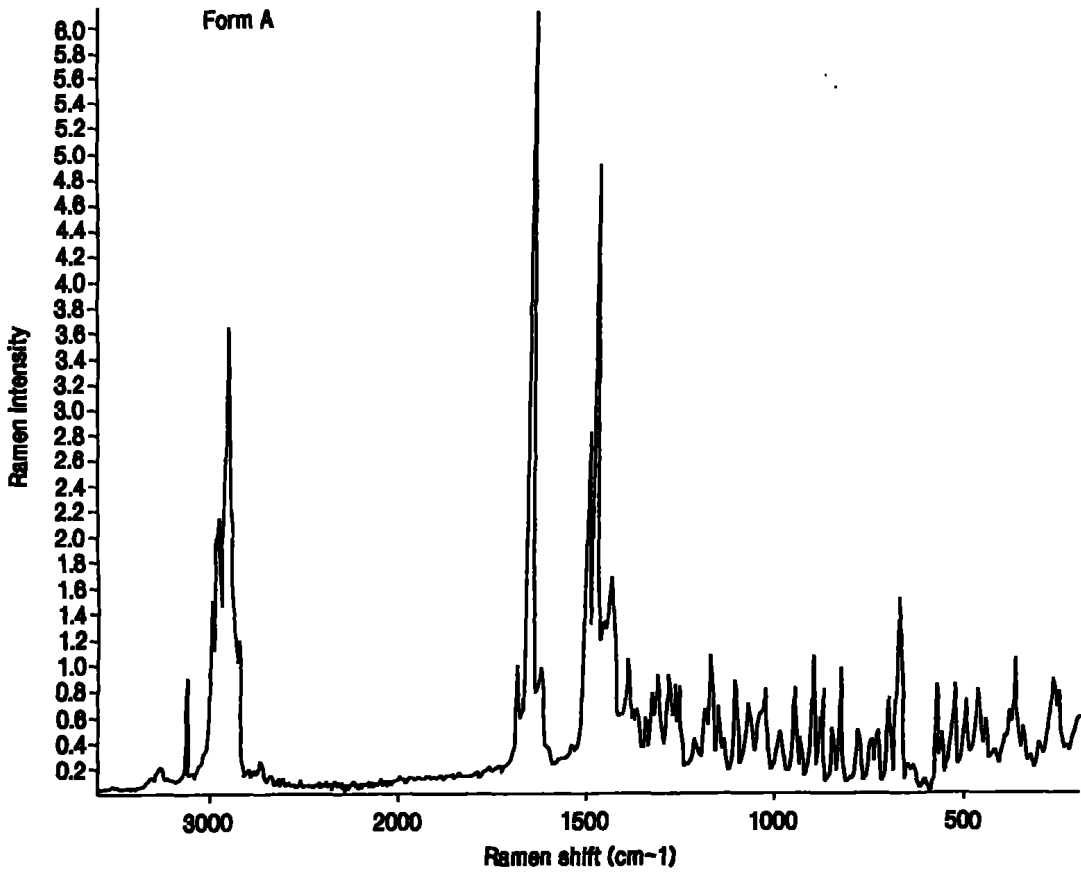


FIG. 5

457

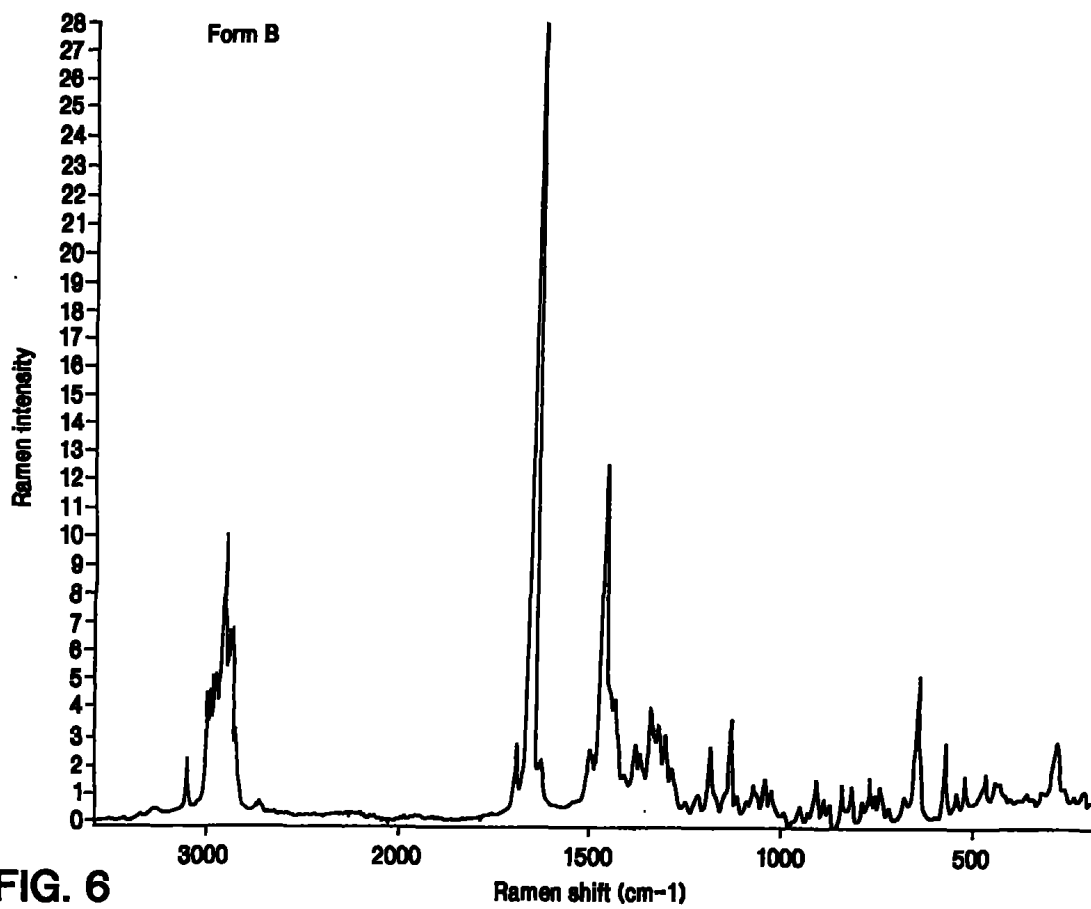
5

WO 02/14323

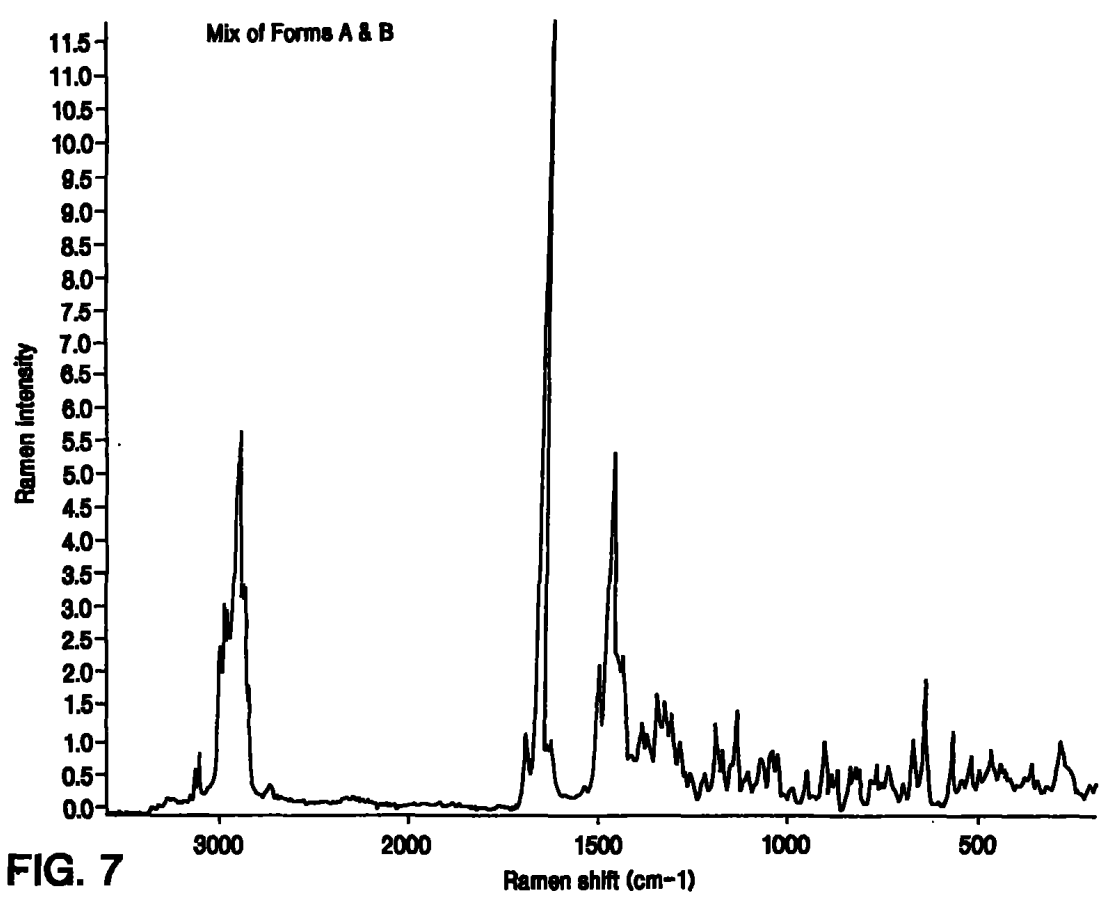
6/9

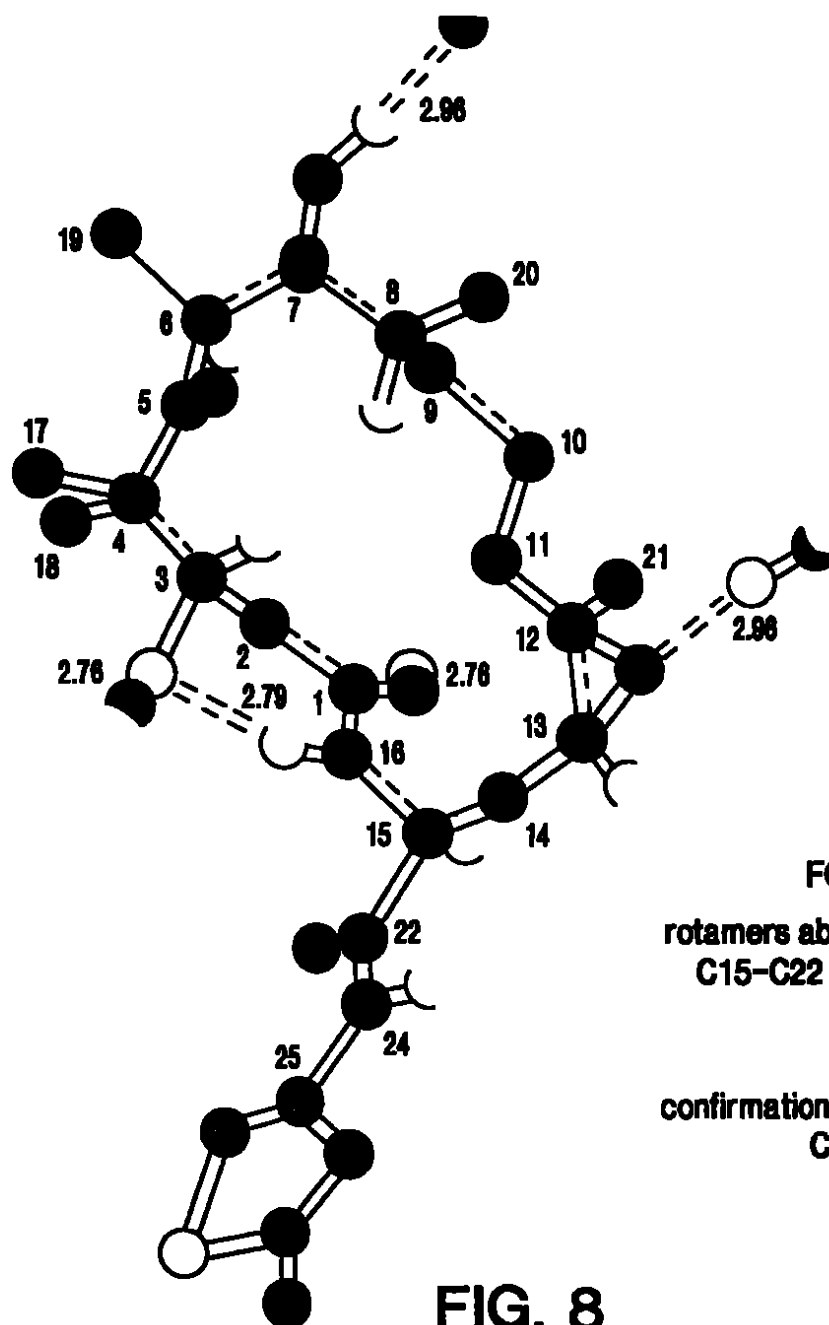
PCT/US01/24540

058



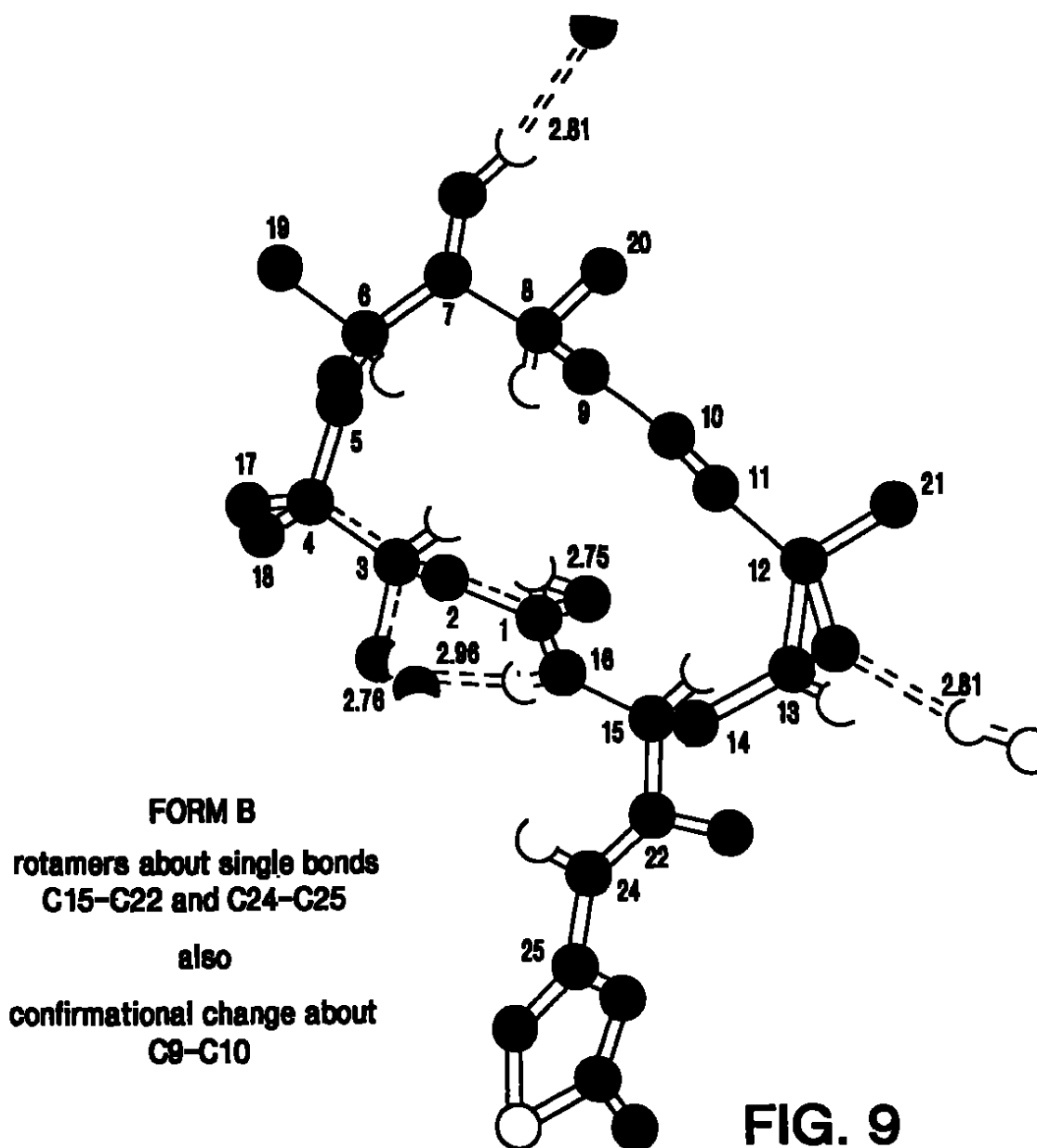
6f





FORM A
rotamers about single bonds
C15-C22 and C24-C25
also
conformational change about
C9-C10

FIG. 8



062



UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FILE FEE REC'D	ATTY. DOCKET NO.	DRAWINGS	TOT CLAIMS	IND CLAIMS
60/225,590 ✓	08/16/2000 ✓		150	LD214	✓ 9		

23914

MARLA J MATHIAS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

FILING RECEIPT



OC000000005538014

Date Mailed: 11/08/2000

Receipt is acknowledged of this provisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the PTO processes the reply to the Notice, the PTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

John D. DiMarco, South River, NJ ; ✓
Jack Z. Gougoutas, Princeton, NJ ; ✓
Imre M. Vitez, Whitehouse Station, NJ ; ✓
Martha Davidovich, East Brunswick, NJ ; ✓
Michael Galella, Belle Mead, NJ ; ✓
Timothy M. Malloy, Yardley, PA ; ✓
Zhenrong Guo, East Brunswick, NJ ; ✓
Denis Favreau, Quebec, CANADA ; ✓

RECEIVED

U.S. Patent Law

NOV 17 2000

Docketed Item _____
Due Date _____
Attorney RP

Continuing Data as Claimed by Applicant

Foreign Applications

If Required, Foreign Filing License Granted 11/07/2000

Title

Polymorphs of an eptothilone analog ✓

Preliminary Class

dr. 11/28/00

TRANSMITTAL LETTER TO THE
UNITED STATES RECEIVING OFFICE

Date	01 August 2001
International Application No.	TBA
Attorney Docket No.	LD214

63

I. Certification under 37 CFR 1.10 (if applicable)

EL800710681US
Express Mail mailing number

01 August 2001
Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Assistant Commissioner for Patents, Washington, D.C. 20231.

<i>Diane C. Bartram</i>
Signature of person mailing correspondence

Diane C. Bartram
Typed or printed name of person mailing correspondence

II. ☒ New International Application

TITLE	POLYMORPHS OF AN EPOTHILONE ANALOG
-------	------------------------------------

Earliest priority date (Day/Month/Year)
16 AUGUST 2000 (16.08.00)

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

- A. ☐ The invention disclosed was not made in the United States.
- B. ☐ There is no prior U.S. application relating to this invention.
- C. ☐ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. (NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority).

application no.	60/225,660	filed on	16 AUGUST 2000 (16.08.00)
application no.		filed on	

- D. ☒ The present international application ☒ is identical ☐ contains less subject matter than that found in the prior U.S. application(s) identified in paragraph C.
- E. ☐ The present international application ☐ contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages and ☐ DOES NOT ALTER ☐ MIGHT BE CONSIDERED TO ALTER the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15

III. ☐ A Response to an Invitation from the RO/US. The following document(s) is (are) enclosed:

- A. ☐ A Request for An Extension of Time to File a Response
- B. ☒ A Power of Attorney (General or Regular)
- C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

- D. ☐ Submission of Priority Documents

Priority document		Priority document	
-------------------	--	-------------------	--

- E. ☒ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ A Request for Rectification under PCT 91 ☐ A Petition ☐ A Sequence Listing Diskette

V. ☐ Other (please specify):

The person signing this form is the:

☐ Applicant	BRISTOL-MYERS SQUIBB COMPANY RENA PATEL PH.D.
☒ Attorney/Agent (Reg. No.) 41,412	Typed name of signer <i>Rena Patel</i>
☐ Common Representative	Signature <i>Rena Patel</i>

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.

64

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) LD214**Box No. I TITLE OF INVENTION**
POLYMORPHS OF AN EPOTHILONE ANALOG**Box No. II APPLICANT**

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.)

BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
LAWRENCEVILLE-PRINCETON ROAD
PRINCETON, NEW JERSEY 08543-4000
UNITED STATES OF AMERICA

☐ This person is also inventor.Telephone No.
(800) 252-5398Facsimile No.
(800) 252-4526

Teleprinter No.

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

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.)

DIMARCO, John D.
16 Neal Drive
East Brunswick, NJ 08816
UNITED STATES OF AMERICA

This person is:

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

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

☒ 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.)

BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
LAWRENCEVILLE-PRINCETON ROAD
PRINCETON, NEW JERSEY 08543-4000
UNITED STATES OF AMERICA
SEE SUPPLEMENTAL SHEET NO. 6

Telephone No.
(800) 252-5398Facsimile No.
(800) 252-4526

Teleprinter No.

☐ 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 APPLICANTS AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet is not to 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.)

GOUGOUTAS, Jack Z.
101 Westerly Road
Princeton, NJ 08540
UNITED STATES OF AMERICA

This person is:

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

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.)

VITEZ, Imre M.
117 Main Street
Whitehouse Station, NJ 08889
UNITES STATES OF AMERICA

This person is:

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

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.)

DAVIDOVICH, Martha
159 Fern Road
East Brunswick, NJ 08818
UNITED STATES OF AMERICA

This person is:

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

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.)

GALELLA, Michael
3 Evergreen Court
Belle Mead, NJ 08502
UNITED STATES OF AMERICA

This person is:

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

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

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

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet is not to be included in the request.</i>	
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.) MALLOY, Timothy M. 1902 Makefield Road Yardley, PA 19087 UNITED STATES OF AMERICA	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
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.) GUO, Zhenrong 21 Augusta Place East Brunswick, NJ 08816 UNITED STATES OF AMERICA	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (that is, country) of nationality: CANADA	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.) FAVREAU, Denis 5065 Terrasse Beaudry Saint-Hubert, Quebec J3Y 6L2 Canada	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (that is, country) of nationality: CANADA	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.) 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
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, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **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, 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 | ☒ GE Georgia | ☒ MW Malawi |
| ☒ AG Antigua and Barbuda | ☒ GH Ghana | ☒ MX Mexico |
| ☒ AL Albania | ☒ GM Gambia | ☒ MZ Mozambique |
| ☒ AM Armenia | ☒ HR Croatia | ☒ NO Norway |
| ☒ AT Austria | ☒ HU Hungary | ☒ NZ New Zealand |
| ☒ AU Australia | ☒ ID Indonesia | ☒ PL Poland |
| ☒ AZ Azerbaijan | ☒ IL Israel | ☒ PT Portugal |
| ☒ BA Bosnia and Herzegovina | ☒ IN India | ☒ RO Romania |
| | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BB Barbados | ☒ JP Japan | |
| ☒ BG Bulgaria | ☒ KE Kenya | ☒ SD Sudan |
| ☒ BR Brazil | ☒ KG Kyrgyzstan | ☒ SE Sweden |
| ☒ BY Belarus | ☒ KP Democratic People's Republic of Korea | ☒ SG Singapore |
| ☒ BZ Belize | ☒ KR Republic of Korea | ☒ SI Slovenia |
| ☒ CA Canada | ☒ KZ Kazakhstan | ☒ SK Slovakia |
| ☒ CH & LI Switzerland and Liechtenstein | ☒ LC Saint Lucia | ☒ SL Sierra Leone |
| ☒ CN China | ☒ LK Sri Lanka | ☒ TJ Tajikistan |
| ☒ CO Colombia | ☒ LR Liberia | ☒ TM Turkmenistan |
| ☒ CR Costa Rica | ☒ LS Lesotho | ☒ TR Turkey |
| ☒ CU Cuba | ☒ LT Lithuania | ☒ TT Trinidad and Tobago |
| ☒ CZ Czech Republic | ☒ LU Luxembourg | |
| ☒ DE Germany | ☒ LV Latvia | ☒ TZ United Republic of Tanzania |
| ☒ DK Denmark | ☒ MA Morocco | ☒ UA Ukraine |
| ☒ DM Dominica | ☒ MD Republic of Moldova | ☒ UG Uganda |
| ☒ DZ Algeria | | ☒ US United States of America |
| ☒ EE Estonia | ☒ MG Madagascar | ☒ UZ Uzbekistan |
| ☒ ES Spain | ☒ MK The former Yugoslav Republic of Macedonia | ☒ VN Viet Nam |
| ☒ FI Finland | ☒ MN Mongolia | ☒ YU Yugoslavia |
| ☒ GB United Kingdom | | ☒ ZA South Africa |
| ☒ GD Grenada | | ☒ ZW Zimbabwe |

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

- ☒ .. ECUADOR .. ☐ .. ☐ ..
- ☐ .. ☐ .. ☐ ..

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

Box No. VI PRIORITY CLAIM		☐ Further priority claims are indicated in the Supplemental Box.		
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) 18 AUGUST 2000 (18.08.00)	60/225,580	US		
item (2)				
item (3)				

☒ 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 the present international application is the receiving Office) identified above as item(s): (1)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(a)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY	
Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA/EP	Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year) Number Country (or regional Office)

Box No. VIII CHECK LIST: LANGUAGE OF FILING	
This international application contains the following number of sheets: request : 6 description (excluding sequence listing part) : 21 claims : 5 abstract : 1 drawings : 9 sequence listing part of description : Total number of sheets : 42	This international application is accompanied by the item(s) marked below: 1. ☒ fee calculation sheet 2. ☒ separate signed power of attorney 3. ☐ copy of general power of attorney; reference number, if any: 4. ☐ statement explaining lack of signature 5. ☐ priority document(s) identified in Box No. VI as item(s): 6. ☐ translation of international application into (language): 7. ☐ separate indications concerning deposited microorganism or other biological material 8. ☐ nucleotide and/or amino acid sequence listing in computer readable form 9. ☐ other (specify): TRANSMITTAL LETTER, GENERAL POWER OF ATTORNEYS
Figure of the drawings which should accompany the abstract:	Language of filing of the international application:

Box No. IX SIGNATURE OF APPLICANT OR AGENT	
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). RENA PATEL PH.D.	

For receiving Office use only	
1. Date of actual receipt of the purported international application: 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):	2. Drawings: ☐ received: ☐ not received:
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:

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 purpose 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 purpose 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. IV - Page 1

ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; BUCHHOLZ, Briana; D'AMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; HERMENAUE, Ronald; KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; LOPEZ, Gabriel; MAKUJINA, Shah; MATHIAS, Marla; McNEIL, Scott; MORSE, David; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia; FURMAN, Theodore; KRIEGER, Stuart

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No.

Applicant's or agent's
file reference

LD214

Date stamp of the receiving Office

Applicant

BRISTOL-MYERS SQUIBB COMPANY

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE	240.00	T
2. SEARCH FEE	846.00	S
International search to be carried out by <u>ISA/EP</u>		
(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)		
3. INTERNATIONAL FEE		
Basic Fee		
The international application contains <u>42</u> sheets.		
first 30 sheets	382.00	b1
<u>12</u> x <u>9.00</u> =	108.00	b2
remaining sheets		
Add amounts entered at b1 and b2 and enter total at B	490.00	B
Designation Fees		
The international application contains <u>88</u> designations.		
<u>6</u> x <u>82.00</u> =	492.00	D
number of designation fees payable (maximum 8)		
Add amounts entered at B and D and enter total at I	982.00	I
(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)		
4. FEE FOR PRIORITY DOCUMENT (if applicable)	15.00	P
5. TOTAL FEES PAYABLE	2,083.00	
Add amounts entered at T, S, I and P, and enter total in the TOTAL box	TOTAL	

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

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

DEPOSIT ACCOUNT AUTHORIZATION (this mode of payment may not be available at all receiving Offices)

- The RO/ US ☒ is hereby authorized to charge the total fees indicated above to my deposit account.
- ☒ (this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.
- ☒ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

19-3880

18/07/2001

Deposit Account No.

Date (day/month/year)

Signature

Rena Patel Ph.D.

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) (Names should be indicated as they appear in the request):

BRISTOL-MYERS SQUIBB COMPANY

hereby appoints (appoint) the following person 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.)

ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; BUCHHOLZ, Briana;
 D'AMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; HERMENAU, Ronald;
 KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; LOPEZ, Gabriel;
 MAKUJINA, Shah; MATHIAS, Marla; McNEIL, Scott; MORSE, David; O'BRIEN,
 Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton;
 RYAN, Richard; SHER, Audrey; SWITZER, Joan; WILK-ORESCAN, Rosemarie;
 WINSLOW, Anastasia; BRISTOL-MYERS SQUIBB COMPANY
 FURMAN, Theodore; P.O. Box 4000
 KRIEGER, Stuart Princeton, New Jersey 08543-4000 UNITED STATES OF AMERICA

to represent the undersigned before



all the competent International Authorities



the International Searching Authority only



the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention:

POLYMORPHS OF AN EPOTHILONE ANALOG

Applicant's or agent's file reference:

LD214

International application number (if already available):

filed with the following Office THE UNITED STATES PATENT AND TRADEMARK as receiving Office
 and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) (where there are several applicants, each of them must sign; 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 or this power):

BRISTOL-MYERS SQUIBB COMPANY

Stephen B Davis
 Stephen B Davis
 Patent Counsel

Date:

18-07-01

CERTIFICATION

The undersigned, being the Executive Vice President and General Counsel of Bristol-Myers Squibb Company, hereby designates:

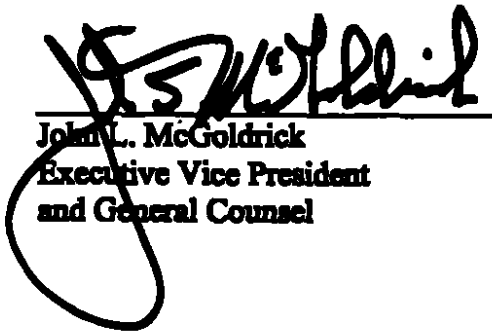
Marla J. Mathias

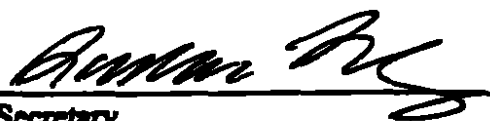
Stephen B. Davis

David M. Morse

(a) to present to the Patent, Trademark, Copyright and similar Government Offices of all countries or to any competent authority, all original, divisional, continuation and reissue applications, petitions and requests in the name of Bristol-Myers Squibb Company and its subsidiary companies, for letters patent for inventions, utility models, industrial models and designs and improvements or additions thereof, trademarks and copyrights: (b) to initiate and prosecute oppositions and appeals: (c) to appear before all officers duly authorized, all Ministers, Bureaus, Clerks' Offices and Commissions or Commissioners that may be necessary: (d) to sign and approve on behalf of this corporation all documents and powers of attorney which in the judgment of the authorized individuals may be necessary or desirable to carry out the powers hereby conferred: (e) to request all proceedings: (f) to pay over or withdraw all taxes, obtain receipts therefor and give discharge: (g) to withdraw applications and all documents relating thereto: (h) to commence proceedings against infringers and assure the defense in infringement actions: and (i) generally to do all that in the judgment of the authorized individual may be necessary to secure the granting of the privileges above-mentioned.

IN WITNESS WHEREOF, I have placed my hand and caused the seal of the Company to be affixed hereto on this 9th day of Dec. 2000.


John L. McGoldrick
Executive Vice President
and General Counsel


Secretary

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

BRISTOL-MYERS SQUIBB COMPANY
Attn. Algieri, Aldo
P.O. Box 4000
Lawrenceville-Princeton Road
PRINCETON, New Jersey 08543-4000
UNITED STATES OF AMERICA

RECEIVED
BMS PATENT LAW

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

FEB 25 2002

(PCT Rule 44.1)

Docketed Item

US 105 5/19/02

Due Date

Attorney

Date of mailing
(day/month/year)

19/02/2002

Applicant's or agent's file reference

LD214

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 01/24540

International filing date
(day/month/year)

01/08/2001

Applicant

BRISTOL-MYERS SQUIBB COMPANY et al.

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

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 48):

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

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

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

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

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

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

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

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

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

Within 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

Chantal Meyer

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 letter to be published for the purpose 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 18 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 206(b)):

The amendments must be submitted with a letter.

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

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

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

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

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

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 48.4)

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

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

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

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

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference LD214	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 01/ 24540	International filing date (day/month/year) 01/08/2001	(Earliest) Priority Date (day/month/year) 16/08/2000
Applicant BRISTOL-MYERS SQUIBB COMPANY et al.		

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

This International Search Report consists of a total of 3 sheets.

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

1. Basis of the report

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

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

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

☐ contained in the international application in written form.

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

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

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

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

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

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

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

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

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

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

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

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 01/24540

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D491/04 A61K31/425 A61P35/00

077

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y ✓	WO 99 42602 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH)) 26 August 1999 (1999-08-26) page 1, paragraph 1 page 10, last four lines of paragraph 1 page 17, paragraph 2 - page 19, last paragraph page 24, paragraph 2 page 25, paragraph 2	1-21
Y	WO 99 27890 A (SQUIBB BRISTOL MYERS CO) 10 June 1999 (1999-06-10) page 1, formula II page 1, line 17 - line 18 page 5, line 13 -page 7, line 2 example 1	1-21



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

12 February 2002

Date of mailing of the international search report

19/02/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 051 epo nl,
Fax (+31-70) 340-3018

Authorized officer

Hoepfner, W

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/24540

078

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

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

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18-21 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. ☐ 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:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/24540

073

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9942602	A	26-08-1999	AU 3028799 A	06-09-1999
			BR 9908119 A	24-10-2000
			CN 1291239 T	11-04-2001
			WO 9942602 A2	26-08-1999
			EP 1054994 A2	29-11-2000
			HU 0100855 A2	28-06-2001
			NO 20004114 A	17-10-2000
			PL 342423 A1	04-06-2001
			SK 12402000 A3	10-05-2001
			TR 200002431 T2	22-01-2001
			US 6194181 B1	27-02-2001
WO 9927890	A	10-06-1999	AU 739380 B2	11-10-2001
			AU 1613499 A	16-06-1999
			EP 1035824 A1	20-09-2000
			WO 9927890 A2	10-06-1999
			ZA 9810993 A	01-06-2000

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/ US

PCT

CHAPTER II

DEMAND

080

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 LD0214	
International application No. PCT/US01/24540	International filing date (day/month/year) 01.08.01 01.August.2001	(Earliest) Priority date (day/month/year) 16.08.00 16.August.00	
Title of invention POLYMORPHS OF AN EPOTHILONE ANALOG			
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.) Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America		Telephone No. 609-252-5398	
		Facsimile No. 609-252-4526	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality: United States of America		State (that is, country) of residence: United States of America	
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.) DIMARCO, John D. 16 Neal Drive East Brunswick, NJ 08816 UNITED STATES OF AMERICA			
State (that is, country) of nationality: US		State (that is, country) of residence: 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.) GOUGOUTAS, Jack Z. 101 Westerly Road Princeton, NJ 08540 UNITED STATES OF AMERICA			
State (that is, country) of nationality: US		State (that is, country) of residence: US	
☒ Further applicants are indicated on a continuation sheet.			

Continuation of Box No. II APPLICANT(S)

081

*If none of the following sub-forms 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.)*

VITEZ, Imre M.
117 Main Street
Whitehouse Station, NJ 08889
UNITED STATES OF AMERICA

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

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

DAVIDOVICH, Martha
159 Fern Road
East Brunswick, NJ 08816
UNITED STATES OF AMERICA

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

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

GALELLA, Michael
3 Evergreen Court
Belle Mead, NJ 08502
UNITED STATES OF AMERICA

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

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

MALLOY, Timothy M.
1902 Makefield Road
Yardley, PA 19067
UNITED STATES OF AMERICA

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

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

☒ Further applicants are indicated on another continuation sheet.

Continuation of Box No. II APPLICANT(S)

082

*If none of the following sub-boxes is used, this sheet is not to 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.)*GUO, Zhenrong
21 Augusta Place
East Brunswick, NJ 08816
UNITED STATES OF AMERICAState (that is, country) of nationality:
CANADAState (that is, country) of residence:
USName 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.)*FAVREAU, Denis
5085 Terrasse Beaudry
Saint-Hubert, Quebec J3Y 6L2
CANADAState (that is, country) of nationality:
CANADAState (that is, country) of residence:
USName and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State (that is, country) of nationality:

State (that is, country) of residence:

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

State (that is, country) of nationality:

State (that is, country) of residence:

☐

Further applicants are indicated on another continuation sheet.

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

PATEL, Rena
 Bristol-Myers Squibb Company
 P.O. Box 4000
 Princeton, NJ 08543-4000
 United States of America

Telephone No.

609-252-5398

Facsimile No.

609-252-4526

Teleprinter No.

Agent's registration No. with the Office
41,412☐ 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:

Box No. VI CHECK LIST

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

- | | | |
|--|---|----------|
| 1. translation of international application | : | 0 sheets |
| 2. amendments under Article 34 | : | 0 sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | 0 sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | 0 sheets |
| 5. letter | : | 0 sheets |
| 6. other (specify) | : | 0 sheets |

For International Preliminary
Examining Authority use only

received	not received
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

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

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

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).

Rena Patel..

Agent

Date: March 7, 2002

Rena Patel

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 80.1(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 IPRA on:

PCT

CHAPTER II

FEE CALCULATION SHEET

Annex to the Demand

85 85

International application No. PCT/US/24540 Applicant's or agent's file reference LD0214 Applicant Bristol-Myers Squibb Company	For International Preliminary Examining Authority use only Date stamp of the IPEA								
CALCULATION OF PRESCRIBED FEES									
1. Preliminary examination fee	750.00 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.)	146.00 H								
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	896.00 TOTAL								
MODE OF PAYMENT									
<table style="width: 100%;"> <tr> <td>☒ authorization to charge deposit account with the IPEA (see below)</td> <td>☐ cash</td> </tr> <tr> <td>☐ cheque</td> <td>☐ revenue stamps</td> </tr> <tr> <td>☐ postal money order</td> <td>☐ coupons</td> </tr> <tr> <td>☐ bank draft</td> <td>☐ other (specify):</td> </tr> </table>		☒ 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 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)									
☒ 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.	IPEA/ <u>US</u> Deposit Account No.: <u>19-3880</u> Date: <u>March 7, 2002</u> Name: <u>Rena Patel</u> Signature: <u>Rena Patel</u>								

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 February 2002 (21.02.2002)

PCT

(10) International Publication Number
WO 02/14323 A3

(51) International Patent Classification⁷: C07D 491/04, A61K 31/425, A61P 35/00

(21) International Application Number: PCT/US01/24540

(22) International Filing Date: 1 August 2001 (01.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 60/225,590 16 August 2000 (16.08.2000) US

(71) Applicant (for all designated States except US):
BRISTOL-MYERS SQUIBB COMPANY [US/US]:
Lawrenceville-Princeton Road, P.O. Box 4000, Princeton,
NJ 08543-4000 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): DIMARCO, John, D. [US/US]: 16 Neal Drive, East Brunswick, NJ 08816 (US). GOUROUTAS, Jack, Z. [US/US]: 101 Westerly Road, Princeton, NJ 08540 (US). VITEZ, Imre, M. [US/US]: 117 Main Street, Whitehouse Station, NJ 08889 (US). DAVIDOVICH, Martha [US/US]: 159 Fern Road, East Brunswick, NJ 08816 (US). GALELLA, Michael [US/US]: 3 Evergreen Court, Belle Mead, NJ 08502 (US). MALLOY, Timothy, M. [US/US]: 1902 Makefield Road, Yardley, PA 19067 (US). GUO, Zhenrong [CA/US]: 21 Augusta Place, East Brunswick, NJ 08816 (US). FAVREAU, Denis [CA/US]: 5065 Terrasse Beaudry, Saint-Hubert, Quebec J3Y 6L2 (CA).

(74) Agents: ALGIERI, Aldo & al.: Bristol-Myers Squibb Company, Lawrenceville-Princeton Road, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(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, GR, GM, GU, HK, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

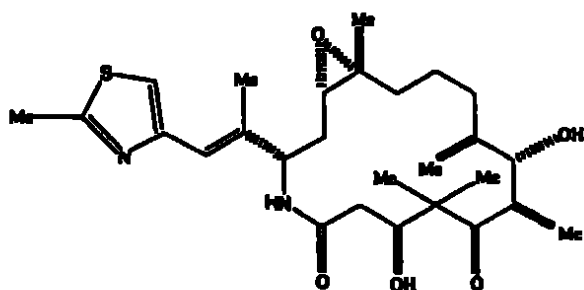
Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
2 May 2002

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: POLYMORPHS OF AN EPOTHILONE ANALOG



(I)

(57) Abstract: There are provided in accordance with the present invention two crystalline polymorphs, designated Form A and Form B, respectively, as well as mixtures thereof, of an epothilone analog represented by formula (I). Also provided are methods of forming the novel polymorphs, therapeutic methods utilizing them and pharmaceutical dosage forms containing them.

WO 02/14323 A3

RECEIVED
BNS PATENT LAW

MAY 14 2002

Docketed item _____

Due Date _____

Attorney _____

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 01/24540

087

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D491/04 A61K31/425 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 42602 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH)) 26 August 1999 (1999-08-26) page 1, paragraph 1 page 10, last four lines of paragraph 1 page 17, paragraph 2 - page 19, last paragraph page 24, paragraph 2 page 25, paragraph 2	1-21
Y	WO 99 27890 A (SQUIBB BRISTOL MYERS CO) 10 June 1999 (1999-06-10) page 1, formula II page 1, line 17 - line 18 page 5, line 13 -page 7, line 2 example 1	1-21



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"A" document member of the same patent family

Date of the actual completion of the international search

12 February 2002

Date of mailing of the international search report

19/02/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentkan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-3040, Tx. 31 851 apo nl,
Fax (+31-70) 340-3018

Authorized officer

Hoepfner, W

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/24540

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9942602	A	26-08-1999	AU 3028799 A	06-09-1999
			BR 9908119 A	24-10-2000
			CN 1291239 T	11-04-2001
			WO 9942602 A2	26-08-1999
			EP 1054994 A2	29-11-2000
			HU 0100855 A2	28-06-2001
			NO 20004114 A	17-10-2000
			PL 342423 A1	04-06-2001
			SK 12402000 A3	10-05-2001
			TR 200002431 T2	22-01-2001
			US 6194181 B1	27-02-2001
WO 9927890	A	10-06-1999	AU 739380 B2	11-10-2001
			AU 1613499 A	16-06-1999
			EP 1035824 A1	20-09-2000
			WO 9927890 A2	10-06-1999
			ZA 9810993 A	01-06-2000

PCT

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

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

ALGERI, Aldo
Bristol-Myers Squibb
Lawrenceville-Princeton Road
P.O. Box 4000
Princeton, NJ 08540-4000
ETATS-UNIS D'AMERIQUERECEIVED
RMS PATENT LAWMAR 05 2002 3/5
MC

Docketed Item

Due Date

Attorney
IMPORTANT NOTICE

R.P.

Date of mailing (day/month/year) 21 February 2002 (21.02.02)		Docketed Item	
Applicant's or agent's file reference LD214		Due Date	
International application No. PCT/US01/24540	International filing date (day/month/year) 01 August 2001 (01.08.01)	Priority date (day/month/year) 16 August 2000 (16.08.00)	
Applicant BRISTOL-MYERS SQUIBB COMPANY et al			

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

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

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

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,

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

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 21 February 2002 (21.02.02) under No. WO 02/14323

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 18 months from the priority date.

It is the applicant's sole responsibility to monitor the 18-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and the PCT Applicant's Guide, Volume II.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.36	Authorized officer J. Zahra Telephone No. (41-22) 338.91.11
--	---

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
- 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	()	()

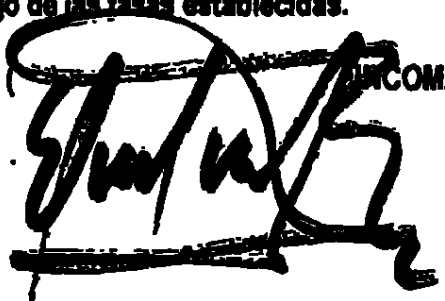
COMPLETA () INCOMPLETA ()

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
Radicacion : 03011545 00000000 Folios: 66
Fecha (000): 2003-02-12 17:06:37
Tramite : 611 PCT-PATENT 370 FASE NNCI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

INFORME DE PROTOCOLO

Expediente N° 03 - 11545.

Fecha: 20 de junio de 2003.

Se certifica que:

Desde fecha 7 de mayo de 1999, del folio 106.177 al folio 106.186 del libro de Protocolo N°

370, obra el poder N° 19.358 conferido por BRISTOL-MYERS SQUIBB COMPANY

domiciliado(a) en Princeton, New Jersey, E.U.A. al doctor RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA.

Representante en Bogotá D.C. Los mismos.

Facultad para desistir y sustituir Si.

Revisado_____.

Al contestar favor indique el número de radicación
consignado en el sticker

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 3 y 10
Sede CAN: Tr. 40A No. 38-50 Correo: 334 12 21-2-3-4
Fon: 281 31 25. Línea 9800-910 163
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia



2020
Bogotá, D.C.,

Doctor:
RAMIRO CASTRO DUQUE
Apoderado
BRISTOL MYERS SQUIBB CO.

Oficio N° 05566

ASUNTO:	Radicación N°	03-11545
	Solicitud Internacional	PCT/US01/24540
	Fecha inicio fase nacional	16/03/2003
	Trámite	011
	Evento	379
	Actuación	330
	Folios	001

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

- ☐ La solicitud no contiene la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT).
- ☐ 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).
- ☐ El solicitante debe aclarar si la solicitud corresponde al capítulo I o II del PCT por que la indicación en el petitorio no es concordante con los documentos del expediente, en caso necesario adjuntar los documentos respectivos.

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 CARMONA CESPÉDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha 18 JUL 2003.