

Señora

Alix Carmenza Céspedes de Vergel

Jefe de División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. _____ S. _____ D. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Referencia: Expediente No. 03.011.545

Solicitud de Patente de Invención titulada: "Polimorfos de un análogo de
epotilona"

Solicitante: Bristol-Myers squibb Company

RESPUESTA AL AUTO NOTIFICADO POR FIJACIÓN EN LISTA NO. 201**DEL 20 DE JUNIO DE 2008, OFICIO NO. 8135 (EXAMEN DE FONDO)**

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia para demostración de lo cual anexo el respectivo poder de abogado y certificación notarial debidamente legalizados y traducidos, doy respuesta al auto emanado por ese Despacho dentro del término legal:

1. Objeciones del Examinador**1.1. De la solicitud de patente.****Descripción**

Sostiene su Despacho que en la descripción solo se encuentran dos ejemplos en los que no se observa ningún efecto inesperado que no sea conocido por el experto, ni ventaja sobre los métodos generales de recristalización ya divulgados.

Se dice, además, que no se encuentran en el capítulo descriptivo, datos comparativos con el estado del arte previo, que indiquen que hay un salto cualitativo.

Reivindicaciones

Se dice que en la reivindicación 1 se menciona “forma caracterizada por” que se debe explicar.

Se dice que la reivindicación 3 se caracteriza un polimorfo cristalino por sus propiedades físico-químicas y no por sus atributos estructurales.

Se dice que en las reivindicaciones 1 a 6 se ha dado la definición del polimorfo por los resultados a alcanzar y no por las características propias del compuesto.

Se establece que en las reivindicaciones 1, 2, 7 y de la 9 a la 13 existen palabras que no delimitan la materia que se desea proteger como “aproximadamente iguales”, “alrededor”, “se calienta una cantidad de 75°C” y otras.

1.2. Novedad

Se considera que el documento WO 99/42602 afectaría la novedad ya que se dice que resulta idéntico al de la presente invención y afectaría el nivel inventivo ya que la presente solicitud de patente sólo tendría una única diferencia con la anterioridad en el proceso de preparación.

Se dice, por otra parte, que el polimorfismo es un fenómeno conocido que se produce de manera espontánea al realizar algunos simples cambios.

Se dice, también, que un polimorfo solo sería nuevo si diera origen a un sistema cristalino distinto.

Se dice, también, que las diferencia en los valores de difracción de RX no implica ventajas técnicas de uno frente a otro y que la obtención de formas “cristalinas” y caracterizadas por Rx no resuelven ningún problema técnico.

2. Respuesta a las objeciones y argumentos a favor de la patentabilidad de la solicitud

Descripción.

Se dice que la descripción sólo posee dos ejemplos en los que no se observa ninguna ventaja ni efecto inesperado.

A este respecto el solicitante desea manifestar lo siguiente:

Sea lo primero aclararle a su Despacho una confusión que da origen a casi todas sus objeciones. El objeto de la presente invención son los polimorfos cristalinos del compuesto de fórmula I que es un **análogo de epotilona B basado en lactama**. El documento D1 se refiere a un polimorfo cristalino de la epotilona B. Le ruego por favor notar que es muy diferente epotilona B que un análogo de epotilona B basado en lactama. A este respecto por favor note la definición dada por el Instituto Nacional de Cáncer de España: "Análogo: en química, sustancia que es similar a otra, pero no idéntica." (subrayado fuera de texto). Esta definición se puede encontrar en:

http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=44919&lang=spanish

De hecho este compuesto (el análogo de epotilona B basado en lactama) para más fácil referencia recibe el nombre genérico de ixabepilona.

Se desea también aclarar que en la presente descripción no hay dos ejemplos sino tres. El ejemplo 2 describe tres procedimientos para preparar la Forma A. En estos procedimientos la forma A se preparó en:

84,3 % de rendimiento con un área HPLC de 99,4;

84,3 % de rendimiento con un área HPLC de 99,7 %, y

88 % de rendimiento con un área HPLC de 99,49.

En comparación, el ejemplo 3 describe tres procedimientos para preparar la Forma B. En estos procedimientos la Forma B se preparó en:

76 % de rendimiento con un área HPLC de 99,6%;
68,8 % de rendimiento con un área HPLC de 98,2, y
60 % de rendimiento con un área HPLC de 99,2.

Claramente, los resultados del ejemplo 2 y 3 muestran una eficiencia mejorada de la Forma A, porque la cristalización le permite a la Forma A ser obtenida con un rendimiento mayor que la forma B, aunque manteniendo la pureza del compuesto medido mediante HPLC. El mayor rendimiento de la forma A es una ventaja inesperada, especialmente en vista de las muchas otras ventajas de la forma A.

Finalmente se desea informar que la presente invención menciona que los cristales de ixabepilona tienen ventaja sobre los materiales amorfos. Por ejemplo, en la página 14, parte final del segundo párrafo, que el cristal de forma A de ixabepilona es más estable que la forma B y que por o tanto se prefiere la forma A.

En cuanto a los datos comparativos con el arte previo por favor note, además, que la solicitud suministra datos de termodinámica y solubilidad para la forma A en la tabla 3. Los datos muestran que la forma A es termodinámicamente más estable como lo evidencia el mayor calor de solución (20,6 kJ/mol), menor solubilidad en agua y solución de polisorbato y mayor densidad cristalina comparado con la forma B. No existe comparación con el material amorfo o no cristalino en razón a que tal material es generalmente no uniforme. Puede haber una gran variación en las propiedades del material amorfo o no cristalino dependiendo de muchos factores experimentales tal como el proceso de aislamiento y el secado del material. El punto clave es que se requiere suministrar un material farmacéutico en una forma física que logre uniformidad y pureza, uniformidad en las propiedades físicas y uniformidad en la estabilidad. La forma A es termodinámicamente más estable que la forma B y por lo tanto esta no se convertirá a la forma B ni a la forma no cristalina durante el almacenamiento. Además, En razón a que la forma A es estable, las propiedades físicas serán aquellas de la forma A y no las propiedades físicas de una mezcla de la forma A y la forma B (o posiblemente una mezcla con material amorfo). Claramente, los cristales de la forma A e ixabepilona tienen propiedades ventajosas sobre otros cristales conocidos y formas no cristalinas de la molécula.

Reivindicaciones.

En respuesta a las diferentes objeciones a las reivindicaciones el solicitante presenta junto

con este escrito un nuevo capítulo reivindicatorio en el cual se han realizado varias modificaciones para hacerlo más claro y responder así a varias de las objeciones.

Para que la anterior modificación surta efecto, adjunto el formulario de modificación voluntaria a solicitud pendiente y la tarifa establecida por ese Despacho para este trámite.

En el nuevo capítulo reivindicatorio se ha hecho una diferenciación en la redacción de los cristales de la Forma A y la Forma B, es decir, las reivindicaciones 1 a 3 están dirigidas a la forma A y las 4 a 6 a la Forma B y la a una mezcla. Las reivindicaciones de proceso (ahora reivindicaciones 8 a 10), están cada una dirigidas a la Forma A y colocadas en forma independiente. Por lo tanto las actuales reivindicaciones se consideran mucho más claras que las originalmente presentadas.

Las reivindicaciones 11 a 14 son nuevas reivindicaciones que citan el polimorfo cristalino de la invención de maneras alternativas, por ejemplo, en la 11 se cita la limitación que el polimorfo esta sustancialmente libre de material amorfo y en la 12 y 14 los niveles de pureza de 98,2 %, 99,2 % y 99,4 %, respectivamente. Todas las anteriores características se encuentran debidamente soportadas en la descripción y por lo tanto no constituyen una ampliación de la misma.

La expresión: “que comprende Forma A caracterizada por”, se ha modificado para mayor claridad por “que comprende la Forma A caracterizada por”.

Las objeciones a las reivindicaciones 3 y luego 1 a 6 no se entienden. Por lo tanto se solicita de manera respetuosa que se aclaren para que si es del caso de den las explicaciones adicionales que se requieran.

Las reivindicaciones 1 a 3 citan respectivamente tres diferentes características físicas del polimorfo cristalino de la Forma A. Cada reivindicación es completa en si misma y cada reivindicación describe una característica física que es diferente de la otra. Se puede decir, por lo tanto, que el polimorfo cristalino de la forma A se caracteriza alternativamente por tres diferentes características físicas. No existe nada impropio en reivindicar diferentes características físicas en diferentes reivindicaciones.

No se entiende como caracterizar un polimorfo por sus características estructurales si como bien lo dice su Despacho la molécula o estructura química de un compuesto con uno o

varios polimorfos es la misma. Los polimorfos se caracterizan por sus diferencias como sus propiedades fisicoquímicas.

No se entiende por qué se dice que los polimorfos cristalinos se caracterizan por los resultados a alcanzar y no por las características propias. Lo que se reivindica son las características propias de cada polimorfo por lo tanto lo de los "resultados a alcanzar" no se entiende.

2.1 Novedad

La novedad de una solicitud está legalmente definida en el Artículo 16 de la Decisión 486 así: *"una invención se considerará nueva, cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso de la prioridad reconocida..."*

De acuerdo con la explicación dada anteriormente debe resultar claro que la presente invención es novedosa: Por lo tanto es solicitante desea reafirma la explicación:

El objeto de la presente invención son los polimorfos cristalinos del compuesto de fórmula I que es un **análogo de epotilona B basado en lactama**. El documento D1 se refiere a un polimorfo cristalino de la epotilona B. Le ruego por favor notar que es muy diferente epotilona B que un análogo de epotilona B basado en lactama. A este respecto por favor note la definición dada por el Instituto Nacional de Cáncer de España: "Análogo: en química, sustancia que es similar a otra, pero no idéntica." (subrayado fuera de texto). Esta definición se puede encontrar en:

http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=44919&lang=spanish

De hecho este compuesto (el análogo de epotilona B basado en lactama) para más fácil referencia recibe el nombre genérico de ixabepilona.

En consecuencia, el objeto de la presente solicitud es novedoso.

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Exempta (P)

Además, D1 reporta el uso de metanol e isopropanol para cristalizar la epotilona B. En contraste la ciclohexanona y el etil acetato son los disolventes preferidos utilizados para la cristalización de la ixabepilona de la presente solicitud. Como se describe aquí, la elección del disolvente es una etapa importante para la exitosa cristalización de la ixabepilona. Adicionalmente, la presente solicitud describe un procedimiento para obtener formas cristalinas de ixabepilona con alto rendimiento y pureza. En la descripción de la presente solicitud (página 8, primer párrafo) se hace referencia al procedimiento de preparación descrito en la solicitud Estadounidense serie número 09/528,526, que se corresponde con la WO 01/70716 (este caso reivindica prioridad de la solicitud Estadounidense serie número 09/528,526 referenciada en la presente solicitud). El procedimiento mencionado (WO01/70716) no produce ixabepilona por vía de un ácido libre intermedio, sino por el contrario, el intermedio correspondiente es una sal, es decir, el intermedio reportado en la página 8 de la presente solicitud (compara con la WO 01/70716 en la página 11, esquema 1). La formación de esta sal intermedia es importante porque posibilita la producción de las formas cristalinas de la ixabepilona tal como se cita.

En cuanto a que el polimorfismo es un fenómeno espontáneo que no tendría ninguna actividad inventiva por favor note lo que se menciona en el artículo titulado: "Relevancia del polimorfismo en el área farmacéutica", escrito por: Elizabeth Sánchez G,^{1,2} Helgi Jung C.², Lilián Yépez M.³, Vicente Hernández-Abad.¹

¹ Laboratorio de Investigación Farmacéutica, Facultad de Estudios Superiores Zaragoza, UNAM;

² Posgrado en Ciencias Químicas, UNAM

³ Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social.

"Los diversos polimorfos de una determinada sustancia suelen presentar comportamientos físico-químicos diferentes en propiedades de interés farmacéutico, por ejemplo: la densidad, la dureza, su tendencia higroscópica, la velocidad de solubilización, la estabilidad térmica o el comportamiento en suspensión, **hecho que puede dar lugar a diferencias importantes en la eficacia de un producto farmacéutico.** Además, **puede resultar muy difícil producir un único polimorfo de forma selectiva,** ya que las energías cristalinas varían muy poco entre polimorfos." (resaltado fuera de texto)

"El polimorfismo puede dotar de nuevas herramientas en el desarrollo de medicamentos, y aún cuando **no se puede predecir qué compuestos presentarán polimorfismo,** se ha observado que, en algunos grupos de fármacos, este fenómeno es muy frecuente, como es el

caso de los barbituratos (70% de las moléculas de este tipo presentan polimorfismo), de las sulfonamidas (60%) y de los esteroides (23%). **El polimorfismo ha contribuido significativamente en el desarrollo de nuevos productos en la industria farmacéutica, química y alimenticia, y continúa proponiendo desafíos a los investigadores en el desarrollo de fármacos y medicamentos**, lo que se convierte en una herramienta única en la ingeniería de sólidos ya que, mediante la manipulación de las estructuras cristalinas y sus propiedades, se puede diseñar un “traje a la medida”, empleando las oportunidades que ofrecen al presentar distintas propiedades físicas, químicas y fisicoquímicas y, de esta manera, resolviendo los desafíos en cuanto al desarrollo del producto así como cumplimiento a las expectativas regulativas.” (resaltados fuera de texto)

Como se podrá notar estas expertas en temas farmacéuticos parecen diferir de manera notoria de la afirmación de su Despacho y muy por el contrario lo que hacen es destacar la importancia del polimorfismo en el desarrollo de nuevos productos farmacéuticos dejando en muy en claro que **“no se puede predecir qué compuestos presentarán polimorfismo”** lo cual indica de manera clara que los polimorfos no sólo son nuevos sino que poseen nivel inventivo.

En cuanto a que un polimorfo sólo sería nuevo si diera origen a un sistema cristalino distinto, esto, hasta donde la ciencia lo conoce actualmente, estaría más allá de las leyes de la fisicoquímica. Se suele decir en el argot popular que “no hay peor ciego que el que no quiere ver”. La discusión que ha rodeado el patentamiento de los polimorfos es una discusión de carácter político y para nada técnico. Las afirmaciones arriba señaladas por las expertas son claras y contundentes. La importancia de los polimorfos en el área farmacéutica se destaca aún más en el siguiente párrafo del mismo artículo de las autoras antes mencionadas: “Las propiedades que se afectan con los cambios en la cristalinidad sirven como una herramienta para modificar las características físicas de las sustancias activas, lo que representa una alternativa atractiva para la investigación farmacéutica en pro de la mejora de los atributos de calidad de los medicamentos”. Me parece que las aclaraciones adicionales sobran.

Se dice, también, que la diferencia en los valores de difracción de RX no implica ventajas técnicas de uno frente a otro y que la obtención de formas “cristalinas” y caracterizadas por RX no resuelve ningún problema técnico. La autora Dra. Sofia Papatoma (Examinadora de patentes (Patent Examiner in Doctorate) de la Oficina Europea de Patentes explica en su presentación: “Patenting Polymorphs at the European Patent office”, en cuanto

a la claridad de una solicitud de patente que verse sobre polimorfos lo siguiente:

“Most suitable for defining a polymorph in a claim are its physicochemical parameters, e.g. those determined by:

- Single crystal X-ray diffraction
- X-ray powder diffraction (XRPD)
- IR- or RAMAN spectroscopy
- ¹³C-NMR spectroscopy
- Thermal methods: TGA, DTA, DSC”

Y adicionalmente agrega lo siguiente: “In most cases, polymorphs are defined in a claim by parameter values, which relate to the physical data used for defining their crystal structure”.

Estimo que con las anteriores consideraciones de la doctora Papathoma queda respondida su afirmación.

Adicionalmente en el artículo titulado “Polimorfismo Farmacéutico” escrito por: África Martín Islán^A y Esther Molina Montes^B (^aLicenciada en Farmacia. Becaria Predoctoral del CSIC y Experta en Polimorfismo de fármacos. ^bLicenciada en Farmacia y en Tecnología de los Alimentos) escrito en la Revista Ámbito Farmacéutico, Vol 25, Número 8, Septiembre de 2006, de OFFARM (Organización Española), se establece lo siguiente:

“Como cada polimorfo presenta propiedades fisicoquímicas características (solubilidad, estabilidad, higroscopicidad), se comporta de forma diferente durante los procesos de liberación, absorción, distribución, metabolismo y eliminación (conocido como proceso LADME). En ocasiones, estas diferencias producen alteraciones importantes en la eficacia del tratamiento. Desde un punto de vista biofarmacéutico y para activos poco solubles, la velocidad de disolución de cada polimorfo será el factor limitante de la absorción y la solubilidad dependerá en cada caso de las energías reticulares del edificio cristalino por la distinta entalpía y punto de fusión que presentan. La utilización de un polimorfo que tenga una adecuada solubilidad proporciona valores sanguíneos suficientes para obtener la acción terapéutica, menos que otra forma menos soluble, al disolverse lentamente y en menor proporción, puede dar lugar a concentraciones sanguíneas insuficientes para lograr una eficacia farmacológica. La elección de una forma cristalina que se disuelva con una alta velocidad alcanzará una concentración plasmática elevada en un intervalo de tiempo

pequeño, y tendrá una concentración mayor a la terapéutica (sobre dosificación) y, consecuentemente provocará toxicidad en el paciente.”

“Un polimorfo puede presentar algunas propiedades indeseables respecto a sus otras formas posibles, que pueden imposibilitar la adecuada preparación industrial de los medicamentos. Aspectos como el grado de solubilidad, fluidez, compresibilidad e higroscopicidad puede imposibilitar operaciones tecnológicas de compresibilidad, pulverización/molienda, liofilización, secado, etc.”

De lo anterior es claro que de un polimorfo no necesariamente se derivan resultados positivos sino que estos pueden ser negativos lo que reafirma aún más el hecho que estos polimorfos deben investigarse y que de ninguna manera es obvio que exista un polimorfo y, aún conociendo su existencia, que este tenga las características que se buscan porque incluso podrán ser negativas. Por lo tanto los polimorfos desarrollados no solo son nuevos sino que poseen nivel inventivo.

2.2 Nivel inventivo

El nivel inventivo de una solicitud se encuentra definido en el Artículo 18 de la Decisión 486 y se establece cuando *“si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica”*.

Contrario a lo que plantea su Despacho, el documento del arte previo citado no afecta el nivel inventivo de la presente solicitud por cuanto no es posible derivar la presente invención dirigida a un polimorfo cristalino de un análogo de epotilona a partir de las enseñanzas presentadas en el documento WO 99/42602, por cuanto dicha patente describe una forma de cristal de la epotilona B, lo cual, como se demostró anteriormente, es un compuesto diferente y por lo tanto no puede afectar ni la novedad ni el nivel inventivo de la presente solicitud.

Por otro lado se ha dado información y explicaciones complementarias sobre por qué los polimorfos no solo son novedosos sino que también poseen carácter inventivo.

La única información complementaria que en este momento deseo agregar es la siguiente:

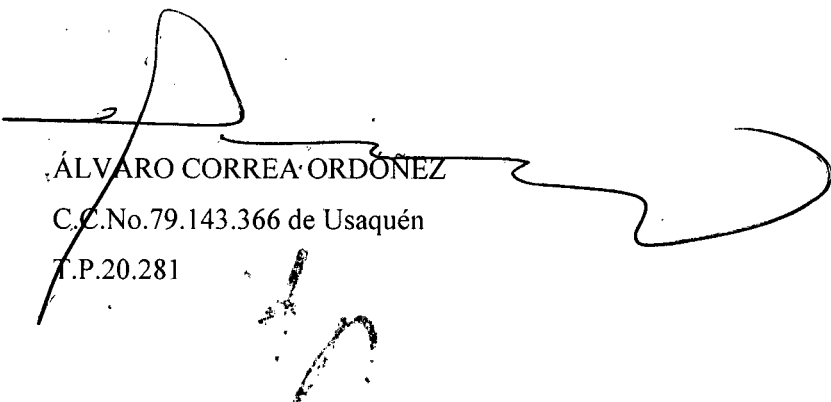
Bajo el expediente 95.023.869 se tramitó la solicitud de patente titulada: "3-[4-(2-aminoetoxi)-benzoil]-2-aril-6-hidroxi[b] tiofeno cristalino" del solicitante Eli Lilly, que trata sobre un polimorfo, a la cual le fue concedido derecho de patente por la Superintendencia de Industria y Comercio de acuerdo con la resolución 20167 de 24 de agosto de 2000. Esto solo con el fin de reafirmar que los polimorfos son patentables y que la misma Superintendencia a concedido derecho de patente sobre los mismos.

3. Solicitudes concedidas en otros países para esta misma invención.

A manera informativa, pongo en conocimiento del Examinador que la patente US 6,689,802, equivalente a la presente solicitud colombiana ha sido otorgada. Aún cuando entiendo que estas decisiones de ninguna manera obligan al Despacho para decidir de igual forma, considero que por tratarse de una pregunta fáctica la determinación de la existencia de novedad, nivel inventivo y aplicación industrial, las decisiones de otras oficinas de patentes constituyen un antecedente persuasivo en la materia.

En virtud de lo anterior, solicito que se acepten las razones expuestas en el presente documento y en consecuencia, se otorgue el privilegio de patente de invención para el invento que se tramita en este expediente.

Atentamente,



ÁLVARO CORREA ORDÓÑEZ

C.C.No.79.143.366 de Usaquén

T.P.20.281

Anexos: Capítulo reivindicatorio modificado
 Formulario de modificación
 Recibo
 Copia de la Patente 6,689,802.
 Poder de abogado y certificación notarial

**(ILICENCIA)
Y PRESENTACION PERSONAL**

Ante el Notario Once del Circulo de Santafé de Bogotá, comparece a

Quien exhibió la C.C. No.

expedida en
y declaró que la firma y huella que aparece
en presente memoria son suyas y que el co-
nido del mismo es cierto.
Memorial dirigido a

Notario de Bogotá, D.C.

Firma del Declarante

HUELLA

Autorizó la anterior Diligencia

16 SEP

16 SEP 2008

REPUBLICA DE COLOMBIA
NOTARIA 11 DEL CIRCULO DE
SANTAFÉ DE BOGOTÁ, D.C.

MONICA Z. BAUTISTA N.
NOTARIA ONCE (E)

146 12

POD-4002

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

PODER OTORGADO POR BRISTOL-MYERS SQUIBB COMPANY

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA
2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:
SALLY B. HANSEN
3. QUIEN ACTÚA EN CALIDAD DE NOTARIO PÚBLICO DE NUEVA JERSEY
4. LLEVA EL SELLO DE:
SALLY B. HANSEN, NOTARIO

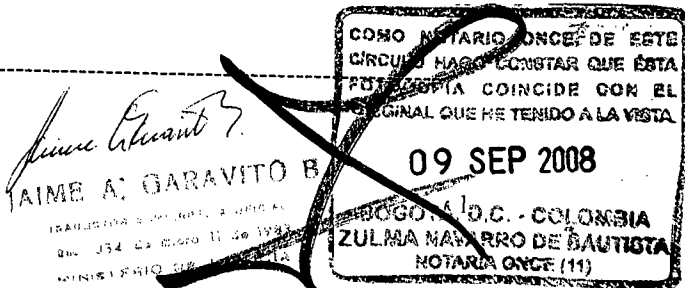
CERTIFICADO

5. EN TRENTON, NUEVA JERSEY
6. EL 28 DE JUNIO DE 2007
7. POR BRADLEY ABELOW, TESORERO DE NUEVA JERSEY
8. N° A295716
9. SELLO (APARECE ADHERIDO SELLO DORADO)
10. FIRMA (FIRMADO) BRADLEY ABELOW

Texto en inglés y en español mediante el cual **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en Nueva York, Nueva York, otorga poder a **ALVARO CORREA ORDOÑEZ y/o OLGA GEORGETTE OTERO y/o RICARDO METKE y/o JUAN PABLO CONCHA**

Dado y suscrito el 30 de mayo de 2007

(Firmado) Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior)



TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

CERTIFICACIÓN NOTARIAL

Texto en inglés y en español mediante el cual el suscrito Notario certifica el 30 de mayo de 2007 la existencia legal de la sociedad **BRISTOL-MYERS SQUIBB COMPANY** así como las funciones y firma de su representante autorizado Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior) para lo cual se basó en los documentos relacionados en inglés en el punto 6 de la certificación los cuales se traducen aquí al español, a saber:

Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.

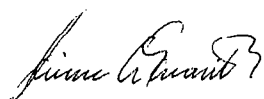
Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado mayo 24, 2005.

[Firmado] SALLY B. HANSEN, Notario Público

[Sello en tinta que dice: "SALLY B. HANSEN. Notario Público de Nueva Jersey. Mi comisión vence el 6 de junio de 2010"]

[Aparece sello realzado]

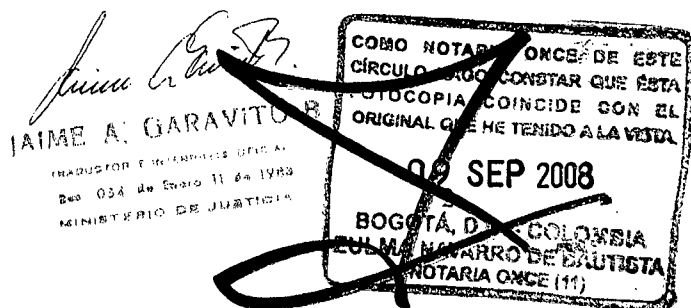
La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.



Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá

Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 82106



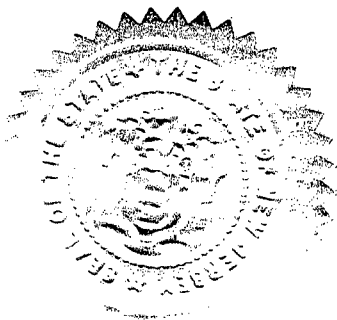
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
SALLY B HANSEN
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
SALLY B HANSEN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 28TH DAY OF JUNE 2007
7. BY: Bradley Abelow, NEW JERSEY TREASURER
8. NO. A295716
9. SEAL/STAMP:
10. SIGNATURE



Bradley Abelow



149 5

BAKER & MCKENZIE

Ralebeck, Lara, Rodríguez & Rueda
Av. 82 No. 10 - 82 8th Floor
Bogotá, Colombia
NIT: 890.088.840-3
Tel: +57 1 634 1500
Fax: +57 1 378 2211
www.bakernet.com

POWER OF ATTORNEY

The undersigned,

BRISTOL-MYERS SQUIBB COMPANY

domiciled in

Route 206 and Province Line Road, Princeton,
New Jersey 08543-4000 United States of America

declares that it hereby grants to

**ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA**

with domicile at Av. 82 No. 10 - 62, 6Th floor, of Bogotá D. C., Colombia, a full and sufficient power of attorney to obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models, industrial designs, integrated circuits, layout-designs and vegetal varieties; the registration of trademarks, denominations of origin, commercial names, trade emblems, slogans and domain names; its renewal, assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Processes of protection to the consumer, unfair competition, oppositions, cancellations, nullity, precautionary injunctions, infringement, granting of licenses, writ mandamus, the protection of trade secrets, and in general the civil, penal, an administrative processes relating to those rights. And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

I hereby ratify all actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 30 day of May of 2007

Signature of the person issuing the Power

Anastasia P. Winslow

Anastasia P. Winslow
Senior Patent Counsel

PODER DE ABOGADO

La abajo firmada,

BRISTOL-MYERS SQUIBB COMPANY

domiciliada en

Route 206 and Province Line Road, Princeton,
New Jersey 08543-4000 Estados Unidos de América

declara por el presente que otorga a

**ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA**

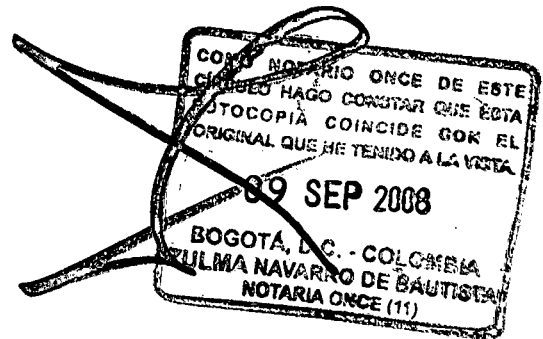
con domicilio en la Av. 82 No. 10 - 62 Piso 6 en Bogotá D. C., Colombia, poder especial amplio y suficiente, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

Igualmente, ratifico todo lo actuado hasta el momento en los mismos asuntos, por cualquiera de los mencionados apoderados en representación de ésta sociedad.

Dado y firmado en

A los 30 días del mes de mayo de 2007

Firma de la persona que firma el Poder



150 16

FAIRER & MURKINER

NOTARIAL CERTIFICATION

On this 30 day of May
2007, the undersigned Notary

CERTIFIES

1. That Name of the person issuing the power
Anastasia P. Winslow
of legal age and domiciled in
Princeton, NJ USA
Address, city, state, country
set his hand on the foregoing document.
2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.
3. That the grantor has executed the foregoing document as
Senior Patent Counsel
Position of the person issuing the Power
of the judicial person **BRISTOL-MYERS SQUIBB COMPANY**
4. That the judicial person **BRISTOL-MYERS SQUIBB COMPANY**
having its home office in
Route 206 and Province Line Road, Princeton,
New Jersey 08543-4000 United States of America
is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.
5. That the grantor has in fact the referred to authority and that his/her representation is legal.
6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
(Please indicate here the documents such as the articles of incorporation, by laws or resolution from the Board of Directors and their dates, on which the notary relied to grant the certification)
- Certification executed by Sr. Vice President and General Counsel of Bristol-Myers Squibb Company on April 7, 2007
- Amended and Restated Certificate of Incorporation of Bristol-Myers Squibb Company dated May 24, 2005

Notary Public
Sally B. Hansen
SALLY B. HANSEN
Notary Public of New Jersey
My Commission Expires June 6, 2010

CERTIFICACION NOTARIAL

A los 30 días del mes de mayo
de 2007, el suscrito Notario

DA FE

1. Que Anastasia P. Winslow
mayor y domiciliado en Princeton, NJ
Estados Unidos de América
suscrió de su puño y letra el documento que antecede.
2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.
3. Que el otorgante ha suscrito el referido documento en su carácter de
Abogados de Patentes Senior
de la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**
4. Que la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**
con sede en
Route 206 and Province Line Road, Princeton,
New Jersey 08543-4000 Estados Unidos de América
está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.
5. Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.
6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:
- Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.
- Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado el 4 de mayo de 2005.

El Notario Público
COMO NOTARIO ONCE DE ESTE CIRCULO NO CONSTAR QUE ESTA COPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
09 SEP 2008
BOGOTÁ, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)



Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

①

SOLICITUD DE

☐

Corrección de Error Material

☒

Modificación de una solicitud

②

SOLICITANTE

Nombre: BRISTOL-MYERS SQUIBB COMPANY

Dirección: P.O. Box 4000, Princeton, NJ 08543-4000, Estados Unidos de América

Nacionalidad o Domicilio: Nueva Jersey, Estados Unidos de América

Lugar de Constitución: Delaware, Estados Unidos de América

Teléfono:

Fax:

E-Mail

IDENTIFICACION

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

③

REPRESENTANTE O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ

Dirección: Avenida 82 No.10-62 Piso 6o.

Teléfono: 634 1500

Fax: 376 2211

E-Mail: patents.bogota@bakernet.com

IDENTIFICACION

C.C.

☒

NIT

☐

C.E.

☐

Otro

☐

Cual

Número 79.143.366

TP 20.281

④

Numero de expediente

03.011.545

⑤

Descripción de la corrección o modificación solicitada

El solicitante presenta capítulo reivindicatorio modificado con

respuesta a auto de fondo No 8135

⑥

Comprobante de Pago No.

08-68760

Fecha 29-AGO-08

⑦

Anexos

☒

Comprobante de pago de la tasa.

☐

Poderes, si fuere el caso.

☐

Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑧

NOMBRE ALVARO CORREA ORDOÑEZ

FIRMA

C.C. 79.143.366

T.P. 20.281

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

2000-F03

2008/016
152 18

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : OR - 68,760
FECHA : AGOSTO 29 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	4672216	29/08/2008	50,501,700.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LENAS COMERCIALES	103,000.00
		TOTAL :	\$ 103,000.00

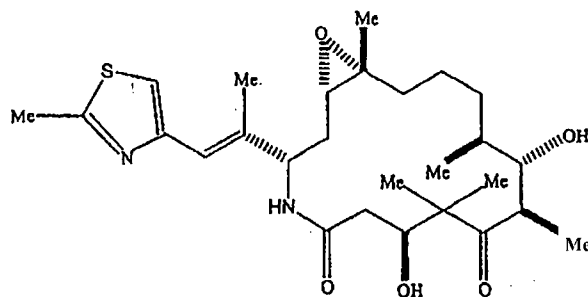
SON: CIENTO TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Reivindicamos:

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



1

que comprende la Forma A caracterizada por:

parámetros de célula unitaria 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/cm³)

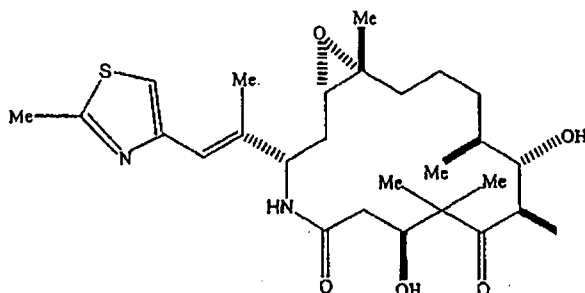
1.247

Punto de Fusión

182-185°C (descomposición)

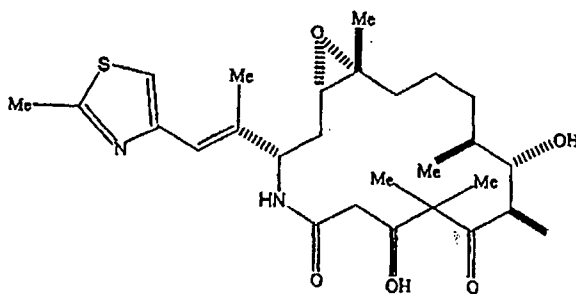
picos característicos en el patrón de difracción de rayos x en polvo a valores de dos teta ($\text{CuK}\alpha \lambda = 1,5406 \text{ \AA}$ a 22°C: 5,69, 6,76, 8,38, 11,43, 12,74, 13,62, 14,35, 15,09, 15,66, 16,43, 17,16, 17,66, 18,31, 19,03, 19,54, 20,57, 21,06, 21,29, 22,31, 23,02, 23,66, 24,18, 14,98,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

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



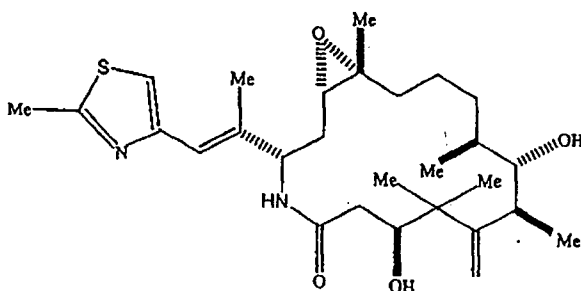
que comprende la forma A caracterizada por una difracción de rayos x en polvo como se muestra en la Fig 1 y un espectro Raman como se muestra en la Fig 5.

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



que comprende la forma A caracterizado por una solubilidad 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.

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

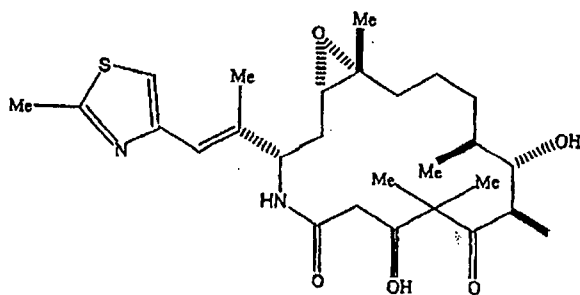


Que comprende la forma B caracterizada por:
parámetros de célula unitaria iguales a lo siguiente:

Dimensiones de Célula	a= 16,675 (2) Å b=28,083(4) Å c=6,054(1) Å Volumen =2835(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

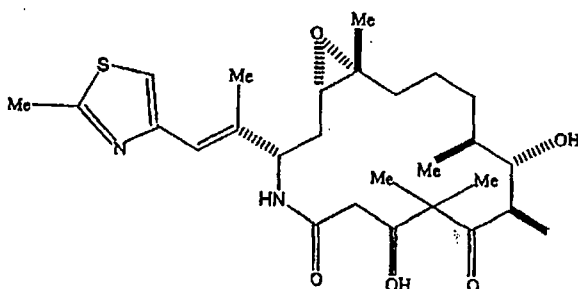
picos característicos en el patrón de difracción de rayos x en polvo a valores de dos teta (CuKα λ=1,5406 Å a 22°C): 6,17, 10,72, 12,33, 14,17, 14,93, 15,88, 16,17, 17,11, 17,98, 19,01, 19,61, 20,38, 21,55, 21,73, 22,48, 23,34, 23,93, 24,78, 25,15, 25,90, 26,63, 27,59, 28,66, 29,55, 30,49 y 31,22.

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



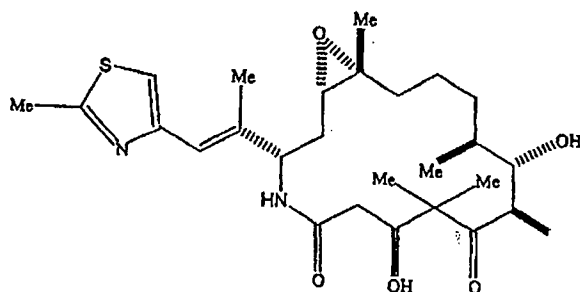
que comprende la Forma B caracterizada por difracción de rayos x en polvo como se muestra en la Figura 2 y un espectro Raman como se muestra en la Figura 6.

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



que comprende la 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.

7. Una composición farmacéutica que comprende un análogo de epotilona representado por la fórmula I:



En donde dicho análogo de epotilona comprende una mezcla del polimorfo cristalino de la Forma A y el polimorfo cristalino de la forma B, en donde la forma A se caracteriza como en las reivindicaciones 1, 2 y/o 3, y la Forma B se caracteriza como en las reivindicaciones 4, 5 y/o 6.

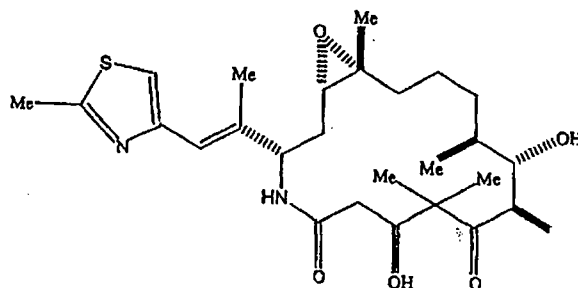
8. Un proceso para producir un polimorfo cristalino que es la Forma A del análogo de epotilona representado por la fórmula I en las reivindicaciones 1, 2 o 3, que comprende calentar un precipitado de dicho análogo representado por la fórmula I en desde 8 a 16 mL de acetato de etilo por gramo de dicho análogo a 75°C manteniendo la temperatura durante una hora, agregando una cantidad de ciclohexano en una relación con respecto a la cantidad de acetato de etilo de desde 1:2 a 2:2, permitiendo que la mezcla se enfríe a temperatura ambiente, manteniendo la mezcla con agitación desde 12 a 96 horas, enfriándola adicionalmente a 5°C durante dos horas y recuperando la Forma A cristalina de allí.

9. Un proceso para producir un polimorfo cristalino que es la Forma A del análogo de epotilona representado por la fórmula I en las reivindicaciones 1, 2 o 3, que comprende calentar un precipitado de dicho análogo representado por la fórmula I en desde 8 a 16 mL de acetato de etilo por

gamo de dicho análogo a 75°C, agregando cristales semilla a éste, manteniendo la mezcla durante 30 minutos, agregando una cantidad de ciclohexano en una relación con respecto a la cantidad de acetato de etilo de desde 1:2 a 2:2, mientras se mantiene la mezcla a 70°C, enfriando la mezcla a temperatura ambiente, manteniendo la mezcla con agitación durante 18 horas, enfriándola adicionalmente a 5°C durante dos horas y recuperando de allí la Forma A cristalina.

10. Un proceso para producir un polimorfo cristalino que es la Forma A del análogo de epotilona representado por la fórmula I en las reivindicaciones 1, 2 o 3, que comprende calentar un precipitado de dicho análogo representado por la fórmula I en desde 8 a 16 mL de acetato de etilo por gamo de dicho análogo a 75°C, durante por lo menos una hora hasta que se forma una solución, enfriando dicha solución a 50°C durante dos horas, agregando allí dichos cristales de semilla cuando la temperatura alcanza 60°C, enfriando la solución a 30°C durante tres horas, reduciendo adicionalmente la temperatura de la solución a —10°C durante tres horas durante una hora de las cuales una cantidad de ciclohexano se agrega allí gota a gota, en una relación con respecto a la cantidad de acetato de etilo de desde 1:2 a 2:2, manteniendo la mezcla resultante a —10°C durante una hora y recuperando de allí la Forma A cristalina.

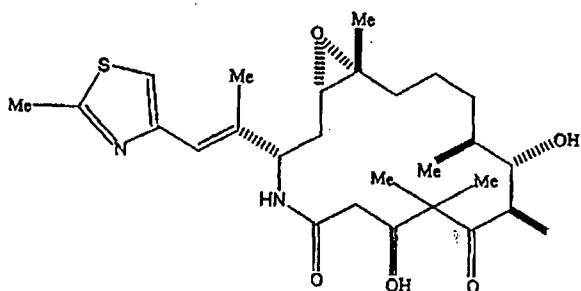
11. Un polimorfo cristalino de un análogo de epotilona representado por la fórmula



dicho polimorfo cristalino esta libre de material amorfo.

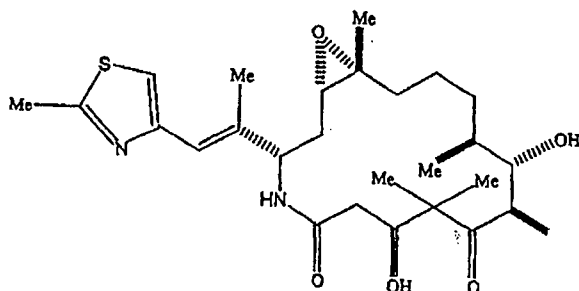
12. Un polimorfo cristalino de un análogo de epotilona representado por la fórmula

158²⁴



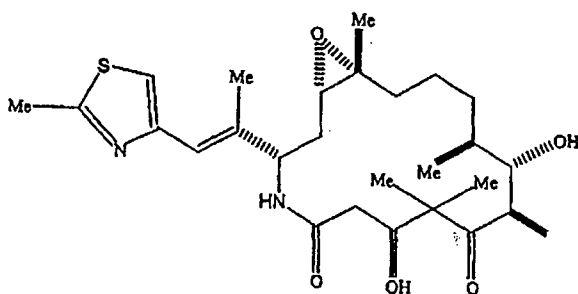
dicho polimorfo cristalino tiene una pureza de por lo menos 98,2 %.

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



dicho polimorfo cristalino tiene una pureza de por lo menos 99,2 %.

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



dicho polimorfo cristalino tiene una pureza de por lo menos 99,4 %.

15. Una composición farmacéutica la cual comprende como ingrediente activo una cantidad efectiva de un polimorfo cristalino tal como se reivindica en una cualquiera de las reivindicaciones 1, 2, 3, 4, 5, 6, 7, 11, 12, 13 o 14.

16. Uso de un polimorfo cristalino para preparar un medicamento para el tratamiento de cáncer en donde el polimorfo cristalino se caracteriza como en las reivindicaciones 1, 2, 3, 4, 5, 6, 7, 11, 12, 13 o 14.



US006689802B2

159 25

(12) **United States Patent**
DiMarco et al.

(10) **Patent No.:** **US 6,689,802 B2**
(45) **Date of Patent:** **Feb. 10, 2004**

(54) **POLYMORPHS OF AN EPOTHILONE ANALOG**

(75) **Inventors:** **John D. DiMarco**, East Brunswick, NJ (US); **Jack Z. Gougoutas**, Princeton, NJ (US); **Imre M. Vitez**, Whitehouse Station, NJ (US); **Martha Davidovich**, East Brunswick, NJ (US); **Michael A. Galella**, Old Bridge, NJ (US); **Timothy M. Malloy**, Yardley, PA (US); **Zhenrong Guo**, East Brunswick, NJ (US); **Denis Favreau**, Saint-Hubert (CA)

(73) **Assignee:** **Bristol-Myers Squibb Company**, Princeton, NJ (US)

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) **Appl. No.:** **09/925,112**

(22) **Filed:** **Aug. 9, 2001**

(65) **Prior Publication Data**

US 2002/0188014 A1 Dec. 12, 2002

Related U.S. Application Data

(60) Provisional application No. 60/225,590, filed on Aug. 16, 2000.

(51) **Int. Cl.⁷** **C07D 493/04; A61K 31/42**

(52) **U.S. Cl.** **514/365; 540/456; 540/462**

(58) **Field of Search** **514/365; 540/462, 540/456**

(56) **References Cited**

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6,204,388 B1 3/2001 Danishefsky et al. 546/340

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DE	19720312	11/1998
DE	19821954	11/1998
DE	19726627	12/1998
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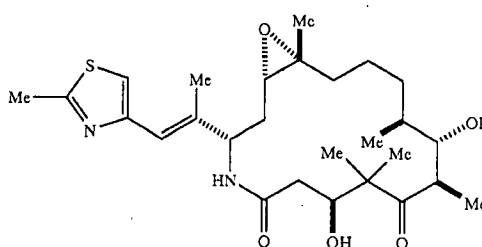
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Primary Examiner—Bruck Kifle

(74) *Attorney, Agent, or Firm*—Rena Patel

(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 the formula



Also provided are methods of forming the novel polymorphs, therapeutic methods utilizing them and pharmaceutical dosage forms containing them.

31 Claims, 9 Drawing Sheets

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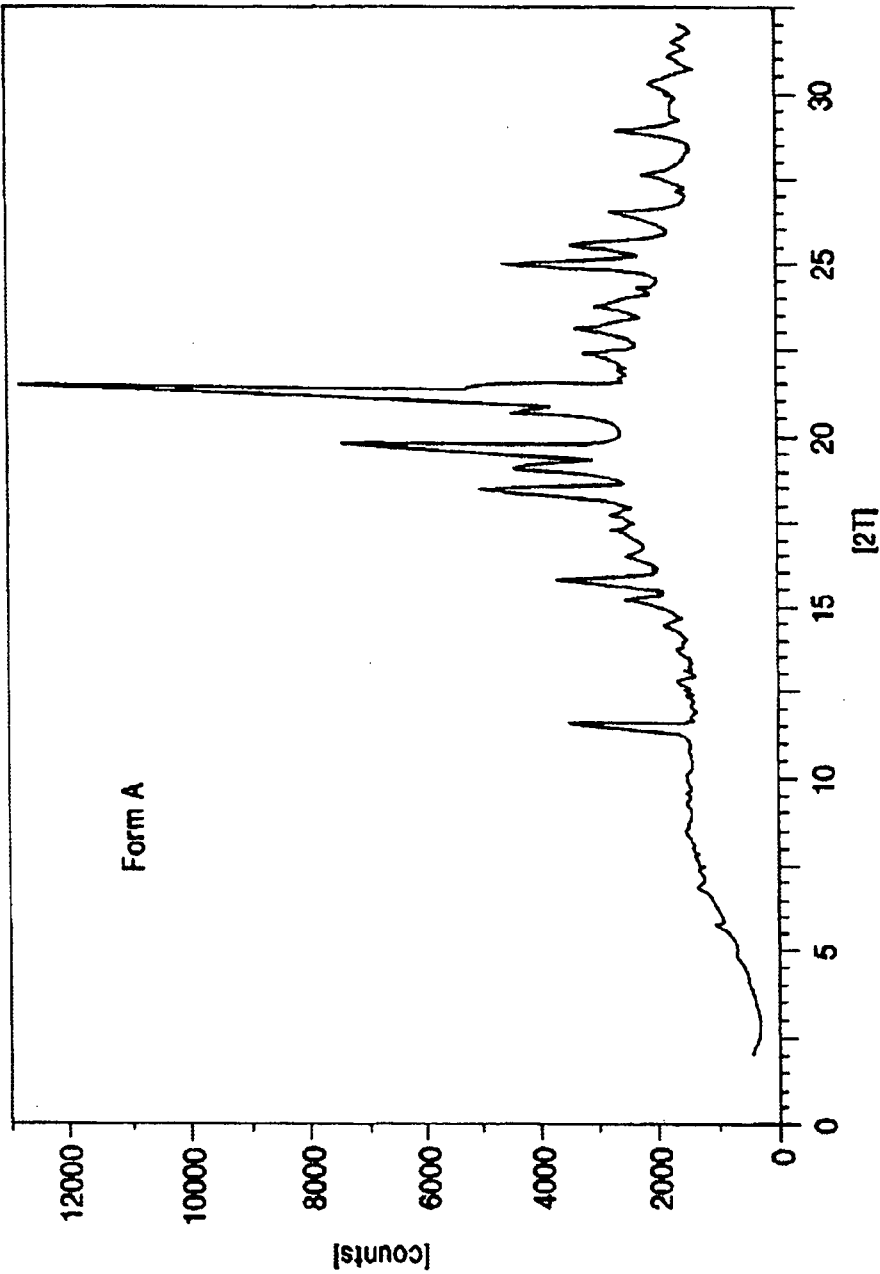


FIG. 1

163 29

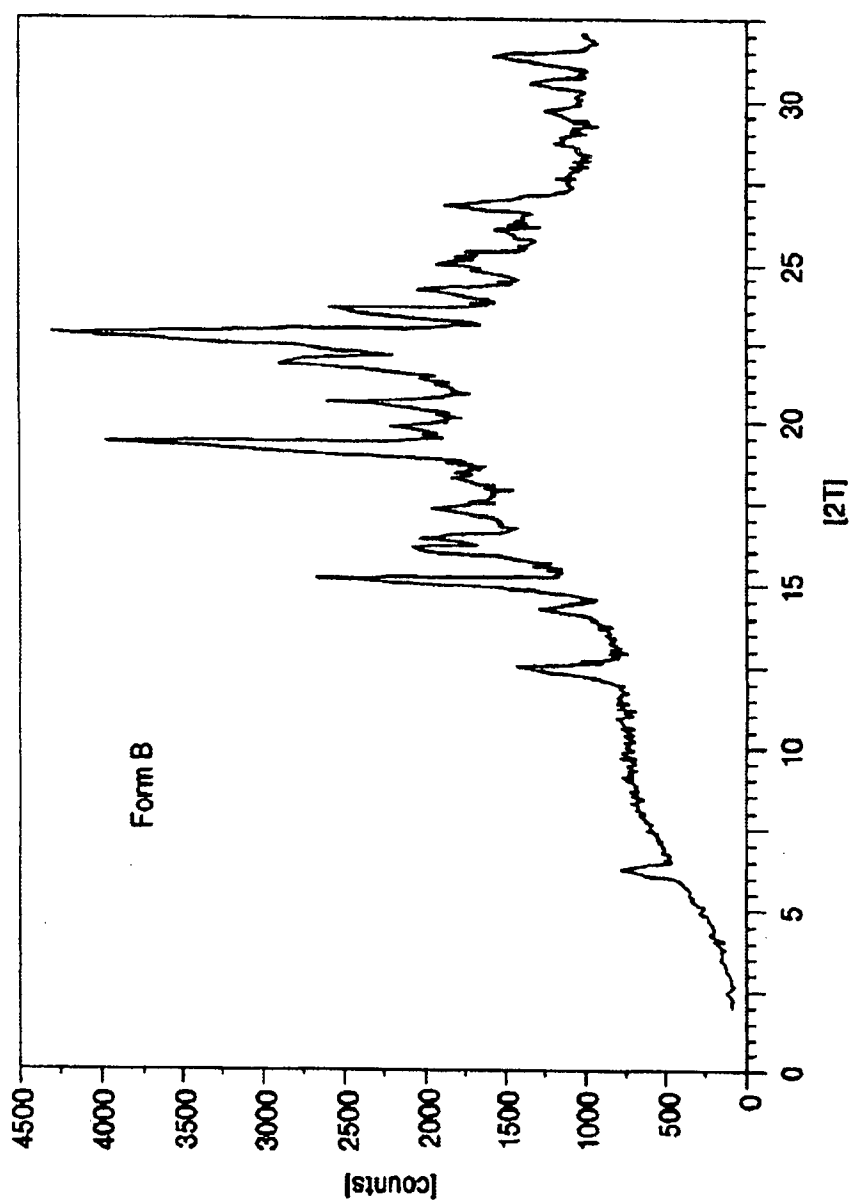


FIG. 2

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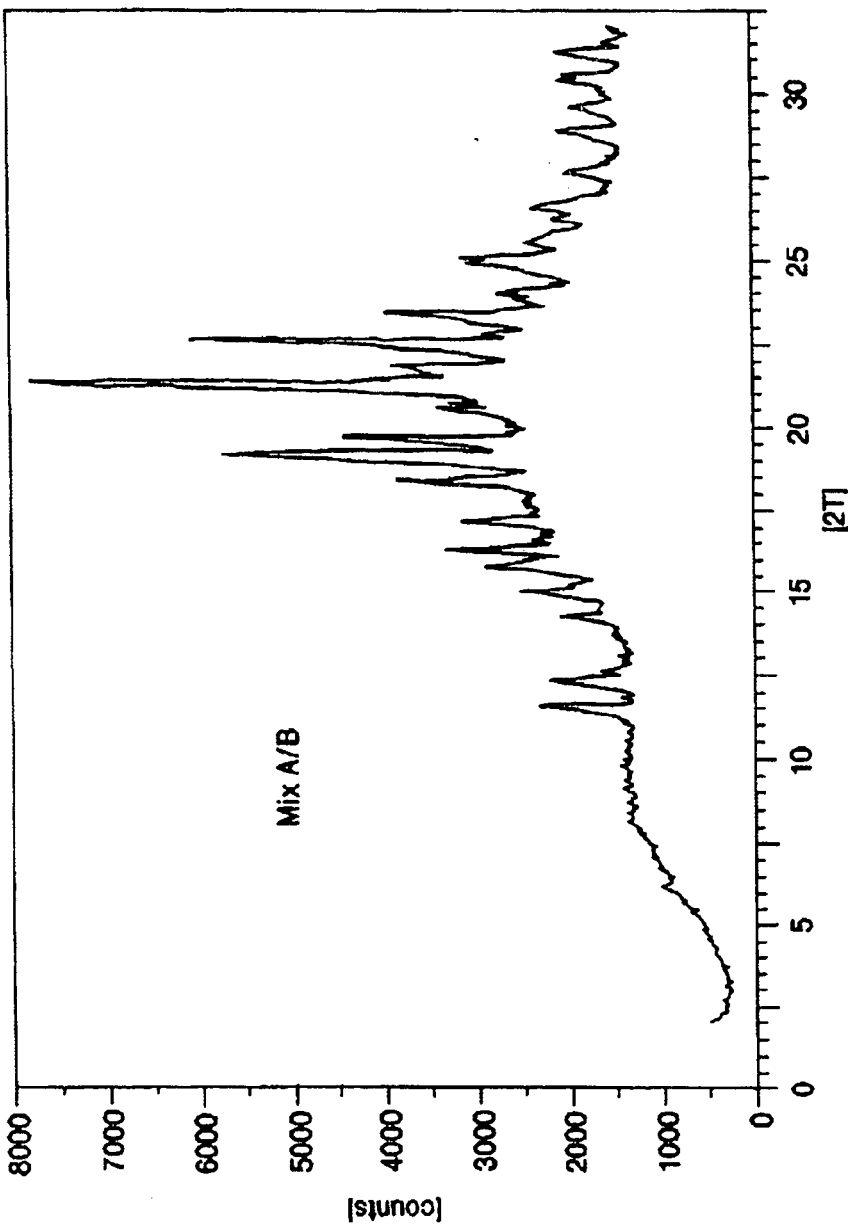


FIG. 3

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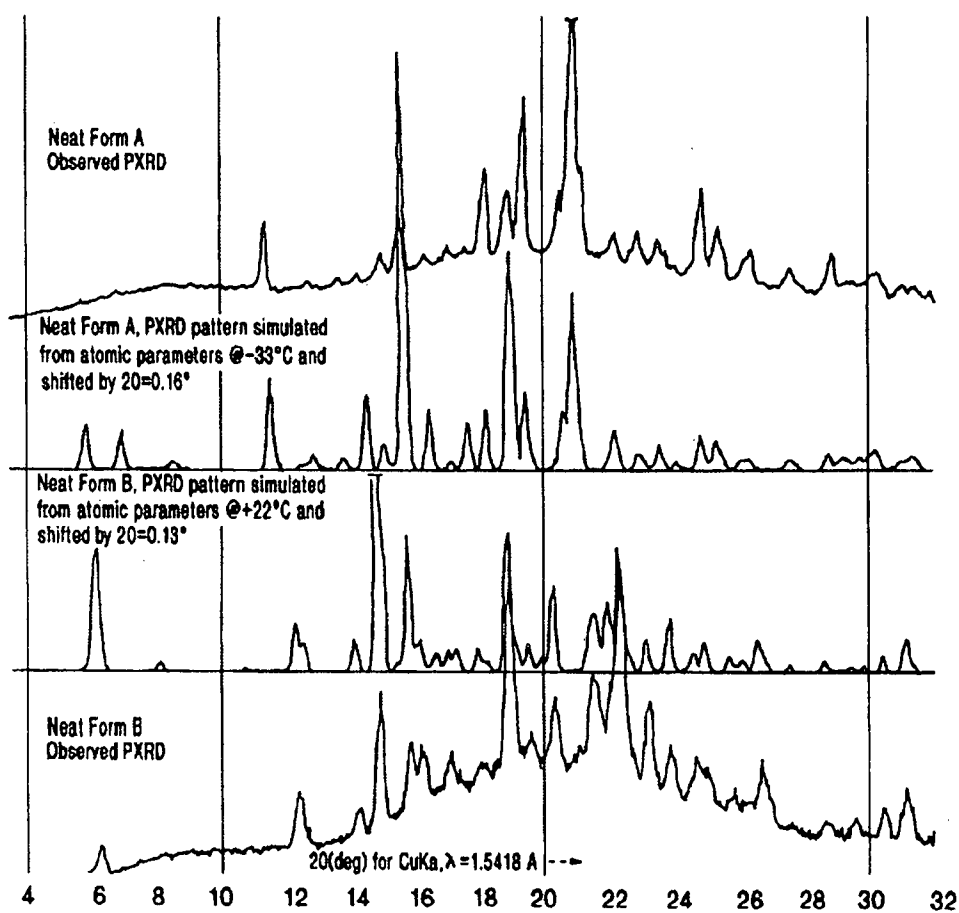


FIG. 4

166 32

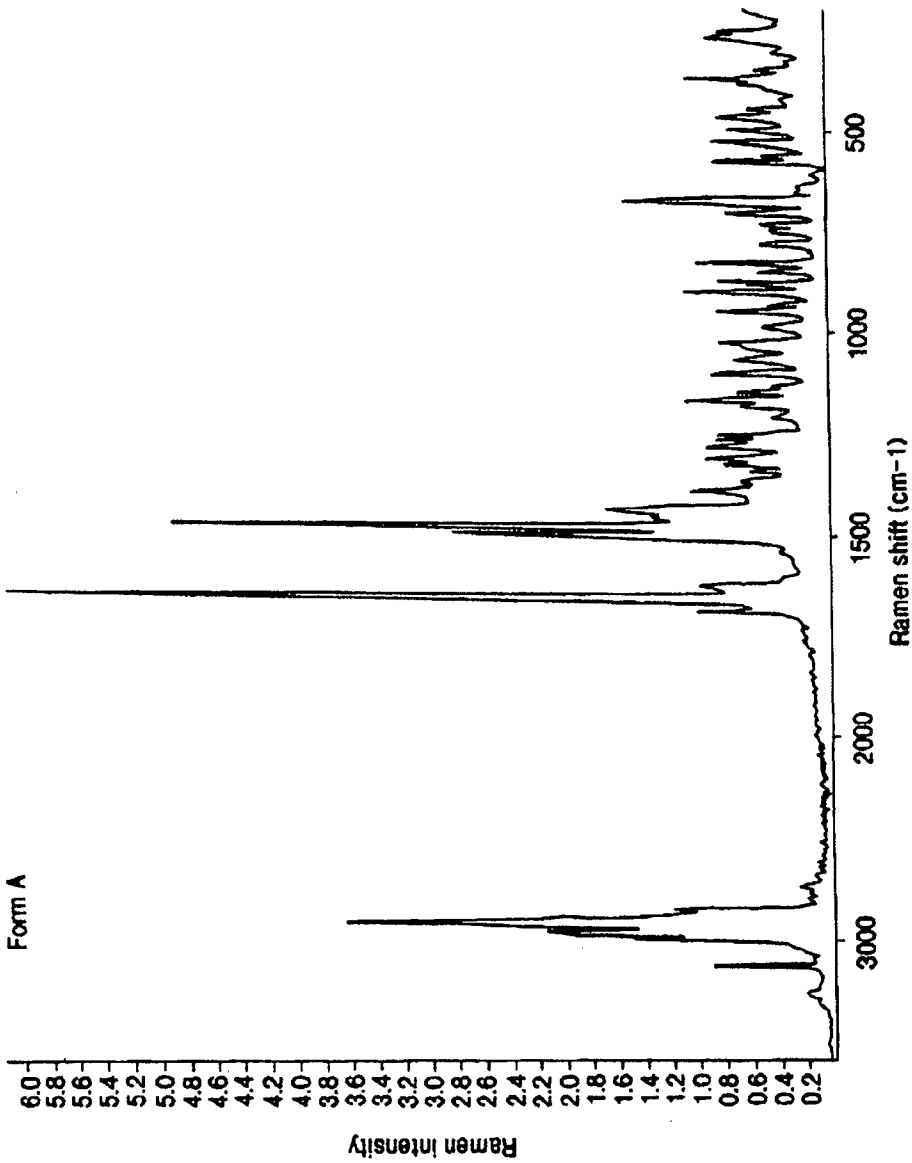


FIG. 5

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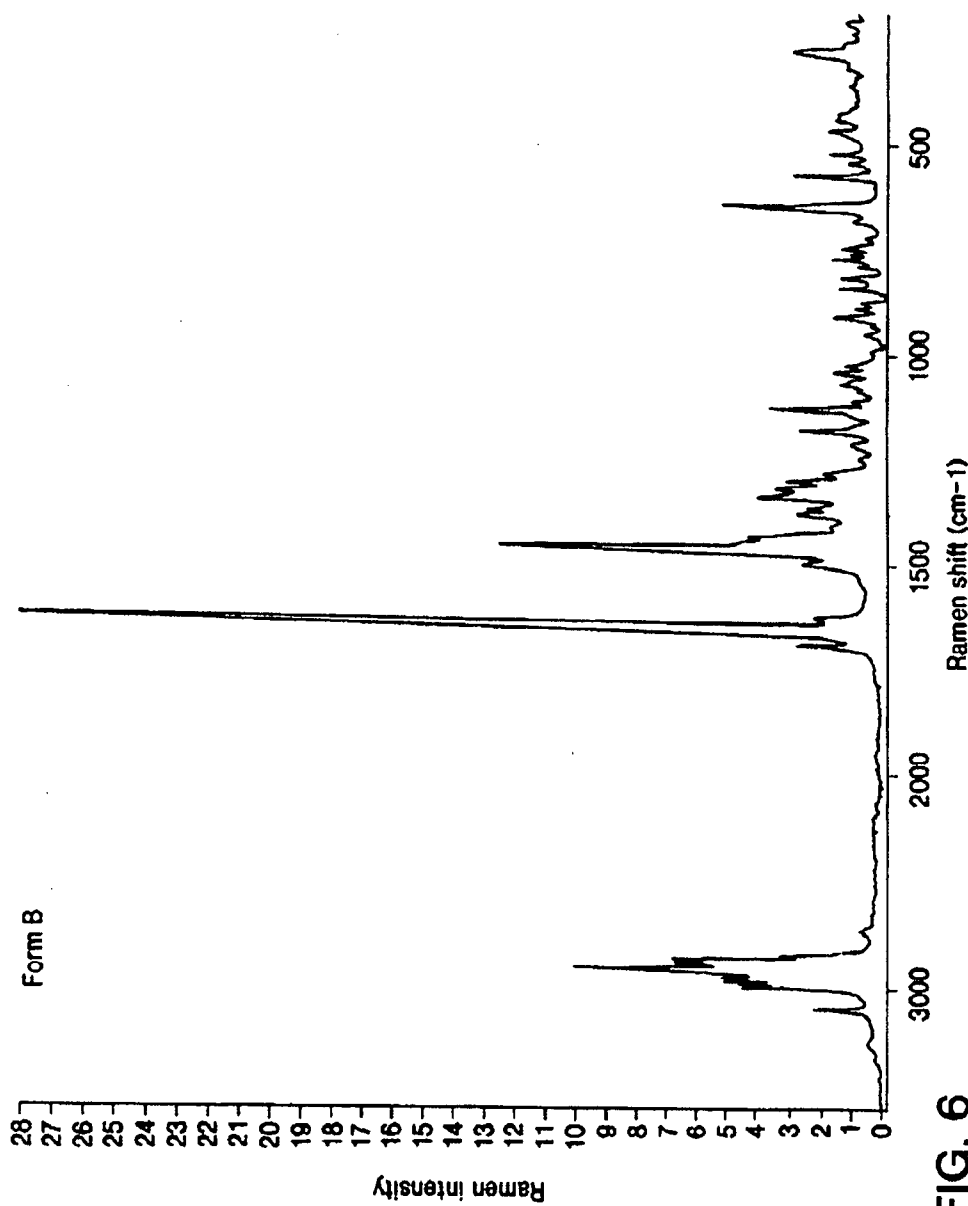
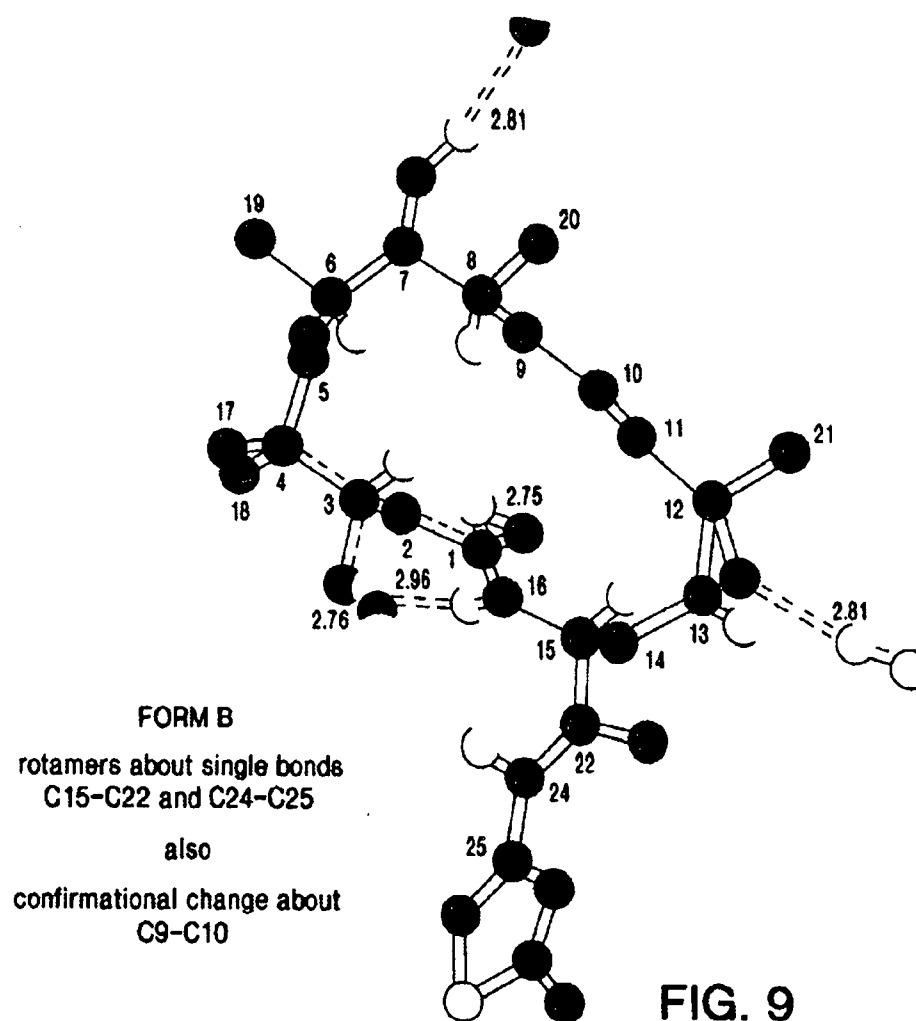
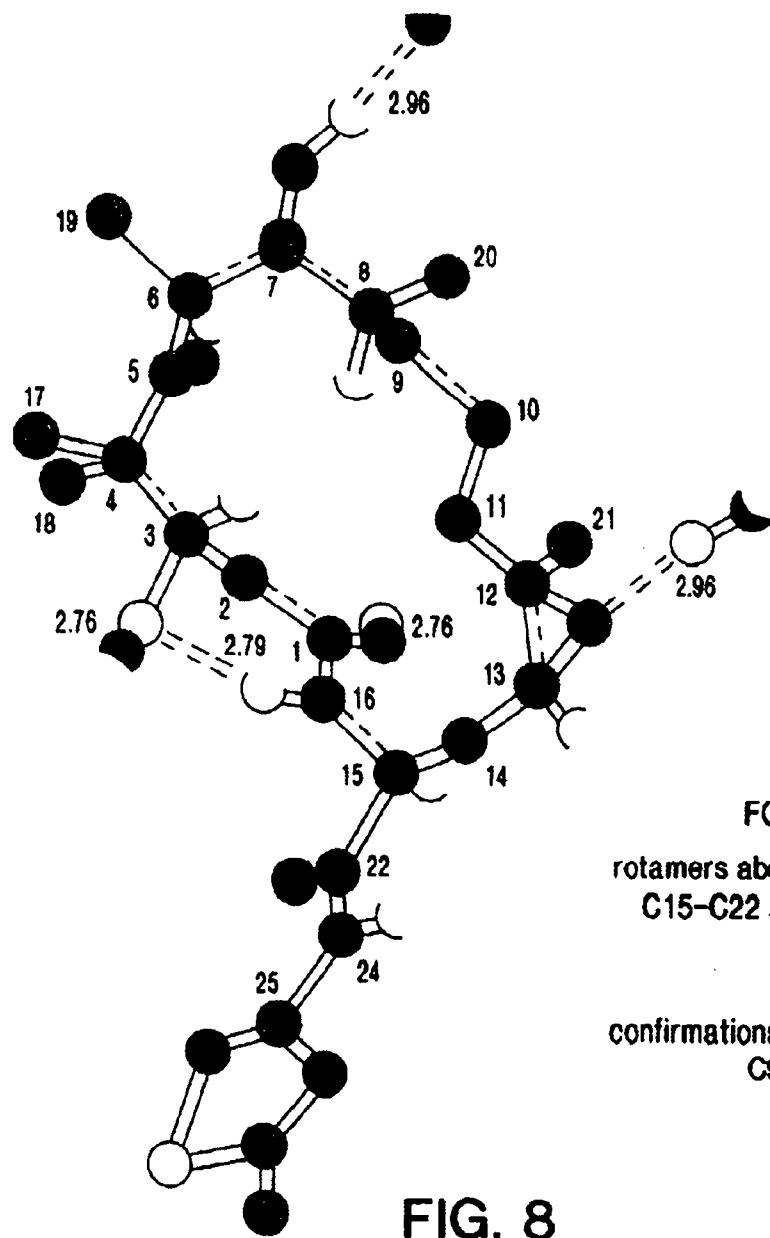


FIG. 6

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34





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

FIG. 8

1

POLYMORPHS OF AN EPOTHILONE
ANALOG

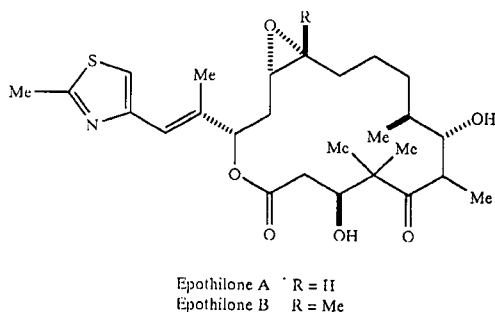
This application claims priority from provisional U.S. application Serial No. 60/225,590, filed Aug. 16, 2000, incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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



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); W093/10121 published May 27, 1993; and W097/19086 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

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.

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.

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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.

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

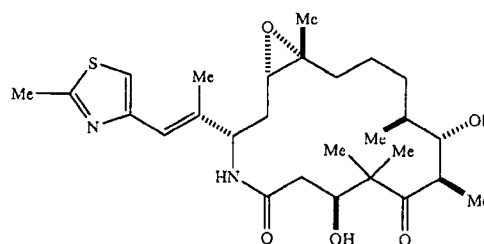
FIG. 7 is a Raman spectrum of a mixture of Forms A and B of the subject epothilone analog.

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

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

SUMMARY OF THE INVENTION

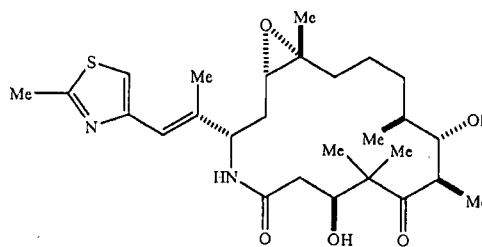
In accordance with the present invention, there are provided two crystalline polymorphs of the epothilone analog represented by formula I.



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



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 Ser. No. 09/170,582, filed Oct. 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 Burkettis 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.

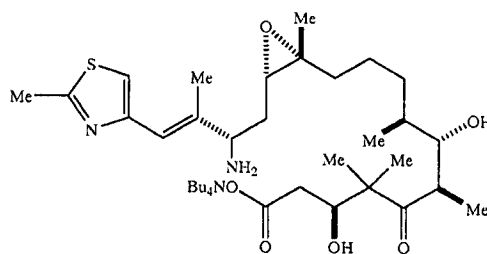
The polymorphs of the analog represented by formula I will induce or inhibit apoptosis, a physiological cell death process critical for normal development and homeostasis. Alterations of apoptotic pathways contribute to the pathogenesis of a variety of human diseases. The subject polymorphs, as modulators 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 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 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, 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; 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 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 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 Ser. 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 Ser. No. 09/528,526 filed on Mar. 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

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38

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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 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, 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 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.

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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. 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.

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 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 44 kV and 40 mA and a CuK α filament of $\lambda=1.5406$ Å 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.

TABLE 1

Values for Form A		
Peak Position (two theta) (CuK α λ = 1.5406 Å at room temperature)	Relative Peak Intensity	
5.69	Very weak	
6.76	Very weak	
8.38	Very weak	
11.43	Weak	
12.74	Very weak	
13.62	Very weak	
14.35	Very weak	
15.09	Very weak	
15.66	Weak	
16.43	Very weak	
17.16	Very weak	
17.66	Very weak	
18.31	Weak	
19.03	Weak	
19.54	Average	
20.57	Weak	
21.06	Very strong	
21.29	Weak	
22.31	Weak	
23.02	Weak	
23.66	Weak	
24.18	Very weak	
24.98	Weak	
25.50	Weak	
26.23	Very weak	
26.46	Very weak	
27.59	Very weak	
28.89	Very weak	

TABLE 1-continued

Values for Form A	
Peak Position (two theta) (CuKα λ = 1.5406 Å at room temperature)	Relative Peak Intensity
29.58	Very weak
30.32	Very weak
31.08	Very 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
6.17	Very weak
10.72	Very weak
12.33	Weak
14.17	Weak
14.93	Average
15.88	Average
16.17	Average
17.11	Average
17.98	Weak
19.01	Very strong
19.61	Average
20.38	Average
21.55	Average
21.73	Average
22.48	Very strong
23.34	Average
23.93	Average
24.78	Average
25.15	Weak
25.90	Weak
26.63	Average
27.59	Very weak
28.66	Weak
29.55	Weak
30.49	Weak
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*, Mac-Millian Co., New York, N.Y. (1968).

	Unit Cell Parameters of Form A	Unit Cell Parameters of Form B
Cell dimensions	a = 14.152(6) Å b = 30.72(2) Å c = 6.212(3) Å Volume = 2701(4) Å ³	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	P2 ₁ 2 ₁ 2 ₁ Orthorhombic
Molecules/unit cell	4	4
Density (calculated) (g/cm ³)	1.247	1.187
Melting point	182–185° C. (decomposition)	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	U22*10e2	U33*10e2	U12*10e2	U13*10e2	U23*10e2
C1	0.3879(3)	0.4352(1)	0.5503(9)	60(6)	25(4)	138(8)	-2(4)	16(5)	-9(4)
O1	0.4055(2)	0.4300(1)	0.7435(5)	68(4)	85(4)	100(5)	6(3)	4(3)	1(3)
C2	0.2864(3)	0.4340(1)	0.4675(7)	42(6)	64(5)	106(6)	0(4)	3(4)	-5(4)
C3	0.2696(3)	0.4210(1)	0.2325(7)	56(6)	44(5)	103(6)	-7(4)	5(4)	13(4)
O3	0.3097(2)	0.4550(1)	0.1027(5)	71(4)	58(3)	128(4)	-6(3)	18(3)	3(3)
C4	0.1615(3)	0.4154(1)	0.1852(7)	50(6)	63(5)	112(6)	-12(4)	-3(4)	7(4)
C5	0.1289(3)	0.3732(1)	0.2895(8)	58(6)	82(6)	103(7)	-6(4)	-13(5)	4(5)
O5	0.0935(3)	0.3748(1)	0.4713(6)	135(6)	83(4)	144(5)	-16(4)	39(4)	5(3)
C6	0.1343(3)	0.3296(1)	0.1769(8)	66(6)	71(5)	118(6)	-13(5)	-7(4)	-10(4)
C7	0.1503(3)	0.2921(1)	0.3353(8)	84(6)	43(5)	134(6)	-27(4)	-2(5)	-10(5)
O7	0.1410(3)	0.2528(1)	0.2127(6)	127(5)	61(4)	163(5)	-34(3)	-17(4)	-9(3)
C8	0.2449(4)	0.2936(1)	0.4540(8)	83(7)	56(5)	127(6)	-26(5)	-4(5)	3(5)
C9	0.3284(4)	0.2824(1)	0.3072(9)	81(7)	68(5)	153(7)	-1(5)	-4(5)	-26(5)
C10	0.4258(4)	0.2877(1)	0.4141(8)	76(7)	56(5)	166(8)	13(5)	-19(5)	-15(5)
C11	0.4467(3)	0.3359(1)	0.4622(8)	67(6)	61(5)	126(7)	-3(4)	-19(4)	-5(5)
C12	0.5220(3)	0.3426(1)	0.6294(8)	53(6)	64(5)	138(7)	16(4)	8(5)	-1(5)
O12	0.6171(2)	0.3288(1)	0.5612(5)	56(4)	61(3)	155(4)	15(3)	8(3)	4(3)

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TABLE 4-continued

Fractional Atomic Coordinates for the Lipothilone Analog of Formula I: Form A									
Atom	X	Y	Z	U11*10e2	U22*10e2	U33*10e2	U12*10e2	U13*10e2	U23*10e2
C13	0.5983(3)	0.3746(1)	0.5991(8)	50(6)	45(5)	162(7)	3(4)	2(5)	-8(5)
C14	0.6099(3)	0.4053(1)	0.4113(8)	47(6)	63(5)	159(7)	2(4)	5(5)	7(5)
C15	0.5568(3)	0.4477(1)	0.4538(8)	44(6)	44(5)	143(6)	-4(4)	7(4)	-1(4)
N16	0.4552(3)	0.4426(1)	0.4005(6)	41(5)	65(4)	106(5)	-3(3)	6(3)	-2(3)
C17	0.1482(4)	0.4138(2)	-0.0603(8)	103(7)	128(7)	104(7)	-29(6)	-10(5)	18(5)
C18	0.1043(4)	0.4539(1)	0.2734(8)	62(6)	67(5)	164(7)	17(5)	9(5)	12(5)
C19	0.0386(4)	0.3232(2)	0.0572(10)	92(8)	115(7)	217(10)	-17(6)	-70(7)	-19(7)
C20	0.2404(5)	0.2630(2)	0.6482(10)	145(9)	114(7)	158(8)	-34(6)	-20(6)	47(6)
C21	0.4974(4)	0.3301(2)	0.8563(9)	109(8)	92(6)	131(7)	19(5)	10(5)	8(5)
C22	0.5935(3)	0.4860(1)	0.3281(8)	48(6)	63(5)	122(6)	6(4)	4(5)	-1(5)
C23	0.5989(4)	0.4815(2)	0.0875(8)	132(8)	78(6)	116(7)	-7(5)	12(5)	-13(5)
C24	0.6154(3)	0.5223(1)	0.4376(8)	59(6)	55(5)	132(6)	-6(4)	9(5)	7(5)
C25	0.6392(3)	0.5656(1)	0.3573(8)	61(6)	65(5)	127(7)	-12(4)	8(5)	5(5)
N26	0.6786(3)	0.5941(1)	0.5076(6)	75(6)	58(5)	129(5)	-9(4)	4(4)	-5(4)
C27	0.6902(3)	0.6325(2)	0.4255(8)	59(6)	69(6)	128(6)	9(4)	2(5)	7(5)
S28	0.6529(1)	0.6381(1)	0.1655(2)	92(2)	79(1)	163(2)	-10(1)	-3(1)	20(1)
C29	0.6196(4)	0.5846(2)	0.1632(9)	85(7)	78(6)	161(8)	-13(5)	-9(6)	3(6)
C30	0.7292(4)	0.6703(2)	0.5523(10)	106(8)	75(6)	186(8)	-29(5)	-5(6)	-10(6)

TABLE 5

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TABLE 5-continued

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

TABLE 6

Fractional Atomic Coordinates for the Epothilone Analog of Formula I: Form B									
Atom	X	Y	Z	U11*10e2	U22*10e2	U33*10e2	U12*10e2	U13*10e2	U23*10e2
C1	0.2316(2)	0.1043(2)	0.7342(8)	56(4)	74(5)	86(6)	5(4)	-6(4)	-16(5)
O1	0.2321(2)	0.1159(1)	0.5376(5)	131(4)	88(3)	74(4)	-24(3)	-13(3)	-7(3)
C2	0.1812(2)	0.0623(1)	0.8106(7)	62(4)	85(5)	68(5)	-7(4)	-6(4)	-22(5)
C3	0.1535(2)	0.0622(1)	1.0506(7)	52(4)	67(4)	71(5)	1(3)	-19(4)	-6(4)
O3	0.2226(2)	0.0539(1)	1.1856(5)	65(3)	123(4)	96(4)	7(3)	-29(3)	-19(4)
C4	0.0876(2)	0.0237(1)	1.0903(7)	63(4)	75(4)	63(5)	5(4)	-4(4)	-10(4)
C5	0.0096(2)	0.0415(1)	0.9838(8)	57(4)	61(4)	78(5)	-7(3)	-2(4)	-10(4)
O5	-0.0132(2)	0.0252(1)	0.8117(6)	100(4)	103(4)	100(4)	19(3)	-38(3)	-38(4)
C6	-0.0409(2)	0.0796(1)	1.1023(6)	53(4)	77(4)	92(6)	14(4)	2(5)	-17(5)
C7	-0.0754(2)	0.1151(1)	0.9373(9)	60(4)	111(4)	185(5)	40(3)	22(4)	-10(4)
O7	-0.1316(2)	0.1434(1)	1.0606(7)	79(3)	74(5)	106(6)	4(4)	8(5)	-14(5)
C8	-0.0135(3)	0.1468(1)	0.8213(8)	75(5)	69(4)	136(7)	-10(4)	-1(5)	-19(5)

TABLE 6-continued

Fractional Atomic Coordinates for the Epothilone Analog of Formula I: Form B									
Atom	X	Y	Z	U11*10e2	U22*10e2	U33*10e2	U12*10e2	U13*10e2	U23*10e2
C9	0.0274(2)	0.1817(1)	0.9812(9)	80(5)	89(5)	175(8)	-21(4)	15(7)	-27(6)
C10	0.0946(3)	0.2107(2)	0.8766(10)	95(5)	98(6)	191(9)	-22(5)	27(7)	-48(7)
C11	0.1389(3)	0.2407(2)	1.0447(11)	97(5)	64(5)	208(9)	-16(5)	10(7)	-28(6)
C12	0.2065(3)	0.2688(2)	0.9440(11)	110(6)	98(4)	241(7)	-36(3)	30(5)	-77(5)
O12	0.2653(2)	0.2862(1)	1.1070(8)	124(4)	82(5)	169(9)	-25(5)	23(6)	-38(6)
C13	0.2894(3)	0.2520(2)	0.9406(10)	104(6)	102(6)	160(8)	-3(5)	-26(6)	-53(6)
C14	0.3190(3)	0.2049(2)	1.0281(10)	117(6)	74(5)	107(6)	-18(4)	-17(5)	-15(5)
C15	0.3253(3)	0.1676(1)	0.8388(8)	86(5)	100(4)	98(5)	-26(3)	-13(4)	-19(4)
N16	0.2738(2)	0.1273(1)	0.8901(7)	64(4)	129(6)	66(5)	-13(5)	-5(5)	10(5)
C17	0.0762(3)	0.0176(2)	1.3416(8)	102(6)	58(4)	113(6)	13(4)	-11(5)	-9(5)
C18	0.1109(2)	-0.0244(1)	0.9909(8)	82(5)	139(7)	187(9)	1(5)	54(6)	29(7)
C19	-0.1098(3)	0.0529(2)	1.2197(10)	79(5)	116(6)	123(8)	10(6)	-19(6)	22(6)
C20	-0.0528(3)	0.1729(2)	0.6272(9)	149(7)	86(6)	338(15)	-8(6)	0(11)	21(9)
C21	0.1829(4)	0.3056(2)	0.7748(15)	175(9)	80(5)	108(6)	-29(4)	-5(5)	-6(5)
C22	0.4128(3)	0.1527(2)	0.7991(8)	80(5)	261(11)	237(13)	28(8)	54(9)	146(11)
C23	0.4521(4)	0.1784(3)	0.6109(13)	141(8)	111(6)	111(7)	-5(5)	3(5)	21(6)
C24	0.4477(3)	0.1216(2)	0.9319(9)	88(5)	96(5)	119(7)	-12(4)	2(5)	-2(6)
C25	0.5303(3)	0.1032(2)	0.9346(9)	76(5)	192(7)	114(6)	2(5)	-6(5)	3(6)
N26	0.5822(2)	0.1091(2)	0.7577(8)	71(5)	165(7)	125(7)	-5(6)	-13(6)	-19(7)
C27	0.6498(3)	0.0890(2)	0.7986(10)	98(6)	128(2)	173(2)	12(1)	-25(2)	0(2)
S28	0.6565(1)	0.0612(1)	1.0487(3)	107(1)	122(6)	166(9)	4(5)	3(6)	43(7)
C29	0.5605(3)	0.0785(2)	1.1053(10)	93(6)	443(17)	150(10)	45(10)	18(7)	-17(12)
C30	0.7206(4)	0.0891(3)	0.6410(12)	102(7)					

TABLE 7

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)
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)

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.

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.

To a jacketed 125 mL round bottom flask, fitted with a mechanical stirrer, there was combined epothilone-B (5.08 g), tetrabutylammonium azide (Bu₄NN₃) (3.55 g, 1.25 equivalents), ammonium chloride (1.07 g, 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 (PMe₃) (1.56 ml, 1.5 equivalents), then tris(dibenzilideneacetone)-dipalladium(0)-chloroform adduct (Pd₂(dba)₃CHCl₃) (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 (NH₄Cl). The filtrate contained (βS, εR, ζS, ηS, 2R, 3S)-3-[(2S, 3E)-2-amino-3-methyl-4-(2-methyl-4-thiazolyl)-3-butenyl]-β, ζ-dihydroxy-γ, γ, ε, η, 2-pentamethyl-6-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

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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.

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/g). The resultant slurry was heated to 75° C. All of solids were dissolved after the slurry was stirred at 75° C. for 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/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 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

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/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 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/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 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

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eluent, HPLC area of 99) and ethyl acetate (183 mL, 10 mL/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/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

[1S-[1R*,3R*(E),7R*, 10S*, 1R*,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/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/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 0.082 g of the title compound, Form B, in 76% yield with an HPLC area of 99.6.

Form—Alternate Procedure

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/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/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 0.315 g of the title compound, Form B, in 68.8% yield with an HPLC area of 98.2.

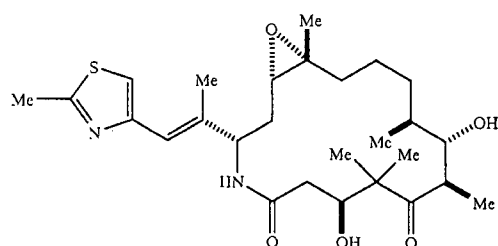
Form B—Alternate Procedure

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 title compound, Form B, in 60% yield with an HPLC area of 99.2.

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We claim:

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



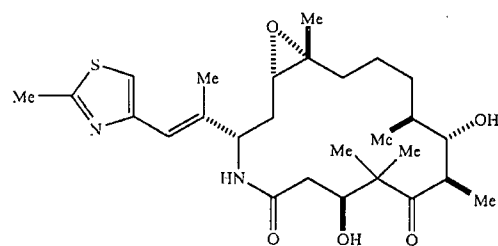
comprising Form A characterized by:

unit cell parameters approximately equal to the following:

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); and

characteristic peaks in the powder x-ray diffraction pattern at values of two theta (CuKα λ=1.5406 Å 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, 14.98, 25.50, 26.23, 26.23, 26.46, 27.59, 28.89, 29.58, 30.32, 31.08 and 31.52.

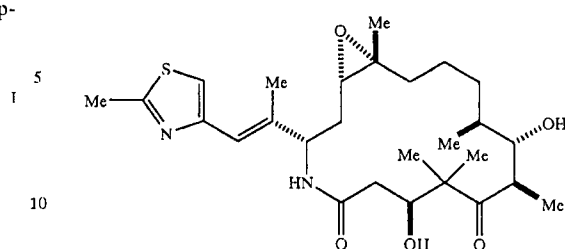
2. A crystalline polymorph of an epothilone analog represented by the formula



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.

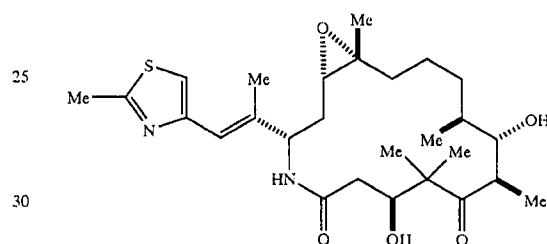
3. A crystalline polymorph of an epothilone analog represented by the formula

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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.

4. A crystalline material of an epothilone analog represented by formula I:



comprising a mixture of Form A and Form B wherein Form A is characterized by:

unit cell parameters approximately equal to the following:

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); and

characteristic peaks in the powder x-ray diffraction pattern at values of two theta (CuKα λ=1.5406 Å 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, 14.98, 25.50, 26.23, 26.23, 26.46, 27.59, 28.89, 29.58, 30.32, 31.08 and 31.52;

and Form B is characterized by:

unit cell parameters approximately equal to the following:

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

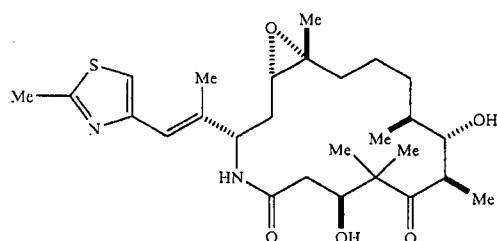
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-continued

Molecules/unit cell	4
Density (calculated) (g/cm ³)	1.187
Melting point	191–199° C. decomposition: and

characteristic peaks in the powder x-ray diffraction pattern at values of two theta (CuK α λ =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, 23.24, 23.93, 24.78, 25.15, 25.90, 26.63, 27.59, 28.66, 29.55, 30.49 and 31.22.

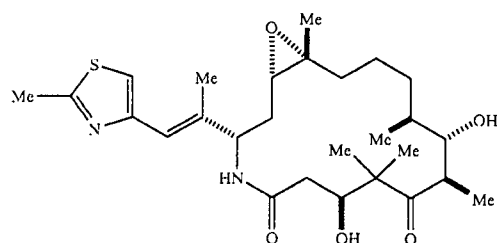
5. A crystalline material of an epothilone analog represented by formula I;



comprising a mixture of Form A and Form B wherein Form A is characterized by powder x-ray diffraction substantially as shown in FIG. 1 and a Raman spectrum substantially as shown in FIG. 5;

and Form B is characterized by powder x-ray diffraction substantially as shown in FIG. 2 and a Raman spectrum substantially as shown in FIG. 6.

6. A crystalline material of an epothilone analog represented by formula I:



comprising a mixture of Form A and Form B wherein Form A is 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; and Form B is 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.

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.

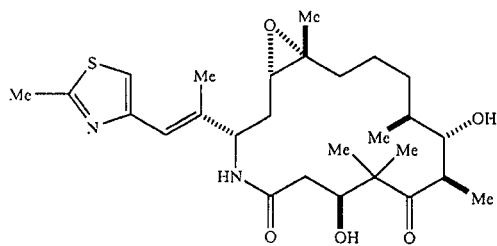
10. A process in accordance with claim 7 wherein said slurry of said analog represented by formula I in ethyl acetate is heated to about 75° C. for at least an hour until a solution is formed, cooling said solution to about 50° C. over about two hours, adding said seed crystals thereto when the temperature 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 8 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.

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



comprising Form B characterized by:

unit cell parameters approximately equal to the following:

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; and

characteristic peaks in the powder x-ray diffraction pattern at values of two theta (CuKα λ=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, 23.24, 23.93, 24.78, 25.15, 25.90, 26.63, 27.59, 28.66, 29.55, 30.49 and 31.22.

14. A process for producing a crystalline polymorph that is Form B of the epothilone analog represented by formula I in claim 13 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.

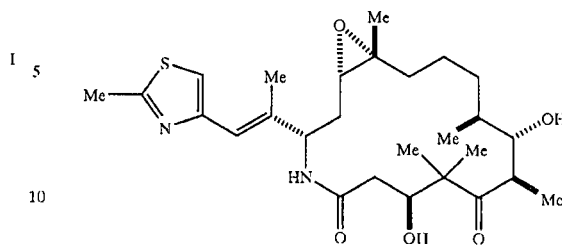
15. A pharmaceutical composition which comprises as an active ingredient an effective amount a crystalline polymorph as claimed in claim 1 and one or more pharmaceutically acceptable carriers, excipients or diluents thereof.

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

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

18. A pharmaceutical composition which comprises as an active ingredient an effective amount of a crystalline polymorph of an epothilone analog represented by formula I:

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and one or more pharmaceutically acceptable carriers, wherein said crystalline polymorph is a mixture of Form A and Form B, wherein Form A is characterized by: unit cell parameters approximately equal to the following:

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); and

characteristic peaks in the powder x-ray diffraction pattern at values of two theta (CuKα λ=1.5406 Å 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, 14.98, 25.50, 26.23, 26.23, 26.46, 27.59, 28.89, 29.58, 30.32, 31.08 and 31.52;

and Form B is characterized by: unit cell parameters approximately equal to the following:

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; and

characteristic peaks in the powder x-ray diffraction pattern at values of two theta (CuKα λ=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, 23.24, 23.93, 24.78, 25.15, 25.90, 26.63, 27.59, 28.66, 29.55, 30.49 and 31.22.

19. 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 claim 1.

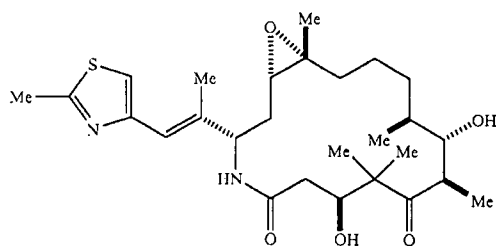
20. A method for treating cancer or other proliferative diseases which comprises administering to a mammal in need thereof an effective amount of a crystalline polymorph as claimed in claim 2.

21. 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 claim 3.

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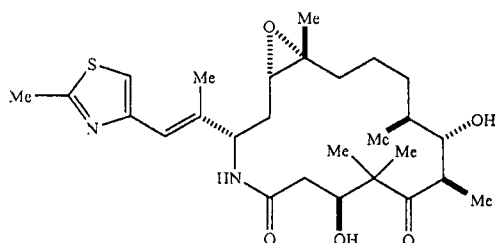
22. A method in accordance with claim 19 wherein said crystalline polymorph is administered parenterally.

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



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

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



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comprising 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.

25. A pharmaceutical composition which comprises as an active ingredient an effective amount a crystalline polymorph as claimed in claim 13 and one or more pharmaceutically acceptable carriers, excipients or diluents thereof.

26. A pharmaceutical composition which comprises as an active ingredient an effective amount a crystalline polymorph as claimed in claim 23 and one or more pharmaceutically acceptable carriers, excipients or diluents thereof.

27. A pharmaceutical composition which comprises as an active ingredient an effective amount a crystalline polymorph as claimed in claim 24 and one or more pharmaceutically acceptable carriers, excipients or diluents thereof.

28. 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 claim 13.

29. 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 claim 23.

30. 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 claim 24.

31. A method in accordance with claim 28 wherein said crystalline polymorph is administered parenterally.

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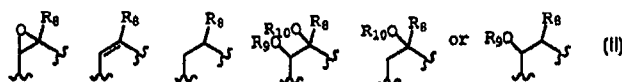
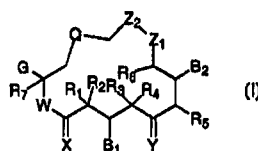
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International Bureau



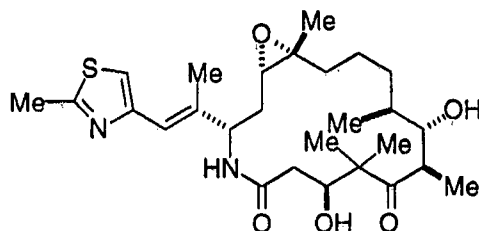
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(54) Title: EPOTHILONE DERIVATIVES



Example 3



5 [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.

A. (3S,6R,7S,8S,12R,13S,15S)-15-Azido-12,13-epoxy-
4,4,6,8,12,16-hexamethyl-7-hydroxy-17-(2-methyl-4-thiazolyl)-5-oxo-
10 16-heptadecenoic acid.

A solution of epothilone B (0.35 g, 0.69 mmol) in degassed THF (4.5 mL) was treated with a catalytic amount (80 mg, 69 mmol) of tetrakis(triphenylphosphine) palladium (0) and the suspension was stirred at 25 °C, under Ar for 30 min. The resulting bright yellow,
15 homogeneous solution was treated all at once with a solution of sodium azide (54 mg, 0.83 mmol) in degassed H₂O (2.2 mL). The reaction mixture was warmed to 45 °C for 1 h, diluted with H₂O (5 mL) and extracted with EtOAc (4 x 7 mL). The organic extracts were washed with saturated aqueous NaCl (15 mL), dried (Na₂SO₄), and concentrated *in vacuo*. The
20 residue was purified by flash chromatography (SiO₂, 3.0 x 15 cm, 95:5.0:0.5 CHCl₃-MeOH-AcOH) to afford Compound A (0.23 g, 61 %) as a colorless oil. MS (ESI⁺): 551 (M+H)⁺; MS(ESI⁻): 549 (M-H)⁻.

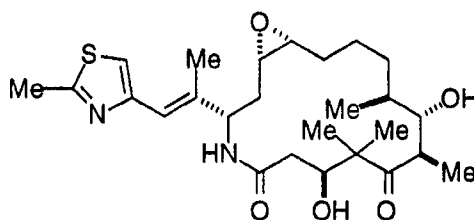
Example 4

Process for reduction of oxirane ring of epothilone and epothilone analogs.

5 To a two-necked flask was added chopped pieces of magnesium turnings (24 mg, 1.0 mmol). The flask was flame-dried under vacuum and cooled under argon. Bis(cyclopentadienyl)titanium dichloride (250 mg, 1.0 mmol) was added followed by anhydrous THF (5 mL). The stirring suspension was evacuated with low vacuum, and the reaction flask was refilled with
10 argon. The red suspension became dark, turning a homogeneous deep green after 1.5h with nearly all the magnesium metal being consumed. An aliquot (3.5 mL, 0.70 mmol, 3.5 eq) was removed and cooled to -78 °C under argon. To this solution was added epothilone A (99 mg, 0.20 mmol, 1.0 eq). The reaction mixture was warmed to room temperature and
15 stirred for 15 min. The volatiles were removed *in vacuo* and the residue was chromatographed two times on silica (25g), eluting with 35% EtOAc/hexanes to give 76 mg (80%) of epothilone C as a pale yellow viscous oil.

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Example 5



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