

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-033799-00007-0000

Fecha: 2009-01-08 16:13:45 Dep: 2020 NULORLACION
Lr: 11 PATENTIA Lve: 379 FASE NACIONAL
Act: 444 RLSPULSTARLOQL Folios: 12

Re: P1.-WYETH.-Solicitud de Patente de Invención en Fase Nacional PCT
para "FORMULACIONES ORALES SÓLIDAS DE
RAPAMICINA 42-ESTER CON ÁCIDO 3-HIDROXI-2-
(HIDROXIMETIL)-2-METIL PROPIÓNICO".-Clase A61K
9/00.-Expediente número 05-033.799.-

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista de 10 de Octubre de 2008.

2. Con el fin de responder a las objeciones expuestas por el señor Examinador en su Concepto Técnico número **2223** bajo los acápites de Claridad de la Solicitud, Novedad y Nivel Inventivo, atentamente me permito presentar los siguientes argumentos técnicos y las siguientes modificaciones a la solicitud, mediante lo cual no sólo se superan dichas objeciones, sino que además se demuestra de forma contundente la patentabilidad de la presente solicitud.

3. **MODIFICACIONES VOLUNTARIAS AL CAPÍTULO REIVINDICATORIO**

Inicialmente me permito manifestar que el solicitante de la invención en cuestión, ha decidido modificar el capítulo reivindicatorio actualmente presentado, realizando los siguientes cambios:

- (i) En la nueva reivindicación 1 se ha establecido que el antioxidante de las composiciones farmacéuticas reveladas está presente en un porcentaje entre 0.01% y 1% en peso, y es seleccionado del grupo que consiste de ácido cítrico, d,l- α -tocopherol, BHA, BHT, monatioglicerol, ácido ascórbico y propil galato.

Dicha modificación encuentra pleno sustento, por ejemplo, en la página 4 (líneas 26 a 29) de la descripción;

- (ii) De conformidad con lo establecido en el punto anterior, las reivindicaciones 7 y 8 también han sido modificadas para establecer que el antioxidante de las formulaciones farmacéuticas reivindicadas se encuentra en un rango entre el 0.01% y el 1% en peso;

(iii) La reivindicación 9 ha sido modificada con el fin de hacerla dependiente de la reivindicación 1; y

(iv) Las reivindicaciones 10 a 19 han sido **eliminadas**.

De conformidad con lo anterior, me permito manifestar que ninguna de las modificaciones realizadas en el capítulo reivindicatorio de la solicitud en cuestión constituye una ampliación de la materia originalmente reclamada, cumpliendo a cabalidad con las disposiciones de patentabilidad establecidas en el Artículo 34 de la Decisión 486 de 2000.

4. CLARIDAD DE LA SOLICITUD

Ahora bien, el señor Examinador ha objetado la claridad de la solicitud en cuestión argumentando lo siguiente:

Descripción

"Se muestra que por granulación húmeda de CCI-779 hay disolución mejorada en agua comparado con cápsulas y tabletas de mezcla seca; pero no se presentan estudios de biodisponibilidad in-vivo de los compuestos con respecto al estado de la técnica que sustenten la ventaja técnica sugerida".

En respuesta a lo anterior, inicialmente me permito señalar que en la página 3 de la descripción claramente se establece que *"un obstáculo hacia la formulación de CCI-779 es su pobre solubilidad acuosa (menos de 1 µg/ml), que hace su biodisponibilidad baja"*, así como también se establece que *"las tabletas de CCI-779 preparadas mediante la compresión directa de CCI-779 no micronizado, con excipientes y rellenos estándar, en presencia o ausencia de surfactantes, proporciona tabletas que no muestran una liberación de fármaco rápida y completa"*.

De conformidad con lo anterior y a partir de la atenta lectura de la presente invención también es claro que el objetivo principal del solicitante fue el de mejorar la solubilidad de las formulaciones de CCI-779, con lo cual también se logra aumentar la biodisponibilidad de dicho principio activo.

Ahora, tal y como se revela en la página 8 de la descripción, el solicitante ha demostrado que las formulaciones de CCI-779 reveladas en la presente invención (las cuales son obtenidas mediante granulación húmeda) muestran una disolución en agua mayor con respecto a las formulaciones de CCI-779 obtenidas mediante granulación en seco, y con respecto al CCI-779 puro.

En vista de lo anterior, es claro que si bien en la descripción no se revelan datos de biodisponibilidad *in vivo*, --tal y como lo requiere el señor Examinador en su Concepto Técnico--, el solicitante ha proporcionado datos experimentales suficientes para demostrar que las formulaciones de CCI-779 reveladas en la presente invención presentan, de manera sorprendente, una solubilidad acuosa mayor, y por ende, una mayor biodisponibilidad a la mostrada por las formulaciones conocidas en el estado de la técnica.

Ahora bien, en este punto resulta de gran importancia resaltar que cualquier libro especializado en ciencias farmacológicas enseña la estrecha relación existente entre la solubilidad de un compuesto activo y su biodisponibilidad. Así, por ejemplo, en el libro "Remington: The science and practice of pharmacy" se establece claramente que para que un fármaco sea absorbido éste inicialmente deber ser solubilizado, por lo que las pruebas de disolución de un fármaco resultan ser de mayor importancia al momento de establecer su biodisponibilidad*.

En consecuencia, atentamente me permito solicitar al señor Examinador la reconsideración de las objeciones realizadas a éste respecto.

Reivindicaciones

- **"Reivindicaciones 1-6: no se define cuáles son los posibles antioxidantes".**

Frente a este particular, me permito reiterar ante ese Despacho que el solicitante ha decidido incluir en la reivindicación 1 una lista específica de los posibles antioxidantes que pueden hacer parte de las formulaciones farmacéuticas reveladas.

De manera específica, en dicha nueva reivindicación 1 se ha establecido que el antioxidante mencionado es seleccionado del grupo conformado por ácido cítrico, d,l- α -tocoferol, BHA, BHT, monotioglicerol, ácido ascórbico y propil galato.

Finalmente, resulta de gran importancia aclarar que la anterior modificación implica adicionalmente a las reivindicaciones 2 a 6, toda vez que dichas reivindicaciones son dependientes de la reivindicación 1.

- **"Reivindicaciones 10-14: se reivindica una composición mediante características esenciales de un proceso por lo tanto equivalen a la reivindicación 9.**

Reivindicación 15: se reivindica una formulación mediante características esenciales de un proceso.

* Remington: The science and practice of pharmacy; Philadelphia college of pharmacy and science; Twentieth edition: 2000; páginas: 995-997.

Reivindicaciones 16-19: Se reivindica una composición dependiente de una reivindicación de formulación. Se requiere unificar términos".

En respuesta a lo anterior, me permito manifestar que el solicitante ha decidido **eliminar las reivindicaciones 10 a 19** actualmente presentadas, con lo cual se superan las objeciones realizadas por el señor Examinador a éste respecto.

- **"No se reconocen las diferencias entre la composición de las reivindicaciones 9-14 y la formulación de las reivindicaciones 15-19".**

Frente a este particular, me permito manifestar que el solicitante ha decidido **eliminar las reivindicaciones 10 a 19** actualmente presentadas, con lo cual se superan las objeciones realizadas por el señor Examinador a éste respecto.

5. **ANÁLISIS DE LA NOVEDAD**

De otra parte, el señor Examinador ha objetado la novedad de la reivindicación 9 actualmente presentada basándose en las enseñanzas del documento US 2002/0091137 (D1).

En este sentido, el señor Examinador argumenta básicamente que los elementos característicos de la composición de la reivindicación 9 (composición oral, CCI-779 y granulación húmeda) *habían sido divulgados previamente* en el Estado de la Técnica, y específicamente en la página 3 del documento D1.

5.1 **CONSIDERACIONES RESPECTO AL DOCUMENTO US 2002/0091137 (D1)**

En términos generales, el documento D1 enseña el uso de CCI-779 en el tratamiento de neoplasmas, estableciendo que dicho compuesto activo puede estar contenido dentro de cualquier forma oral convencional (tabletas, cápsulas, etc), y puede estar mezclado con aglutinantes y/o *diluentes inertes farmacéuticamente aceptables*.

Asimismo, dicha anterioridad enseña que las formulaciones de tableta conteniendo CCI-779 pueden ser obtenidas mediante *compresión convencional, granulación húmeda o granulación seca*, utilizando adicionalmente diluentes, enlazantes, lubricantes, desintegrantes, agentes modificadores de superficie y agentes suspensores y estabilizantes.

Ahora bien, con base en lo anterior y con el ánimo de demostrar el carácter novedoso de la nueva reivindicación 9 frente a las enseñanzas del documento D1, inicialmente me permito señalar que, --tal como se mencionó previamente en el

numeral 3 del presente memorial-, el solicitante ha decidido modificar dicha reivindicación 9, haciéndola dependiente de la reivindicación 1. 109

Por lo tanto, es claro que la formulación farmacéutica a la que ahora se hace referencia en la reivindicación en cuestión incluye una granulación caracterizada porque comprende: (i) CCI-779, (ii) un polímero soluble en agua, (iii) un surfactante, (iv) 0.01% a 1% p/p de un antioxidante seleccionado del grupo que consiste de: ácido cítrico, d,l- α -tocoferol, BHA, BHT, monotioglicerol, ácido ascórbico y propil galato, y (v) un agente modificador de pH.

Sin embargo, tal como el señor Examinador lo afirma en su Concepto Técnico, el documento **D1** falla en enseñar una formulación farmacéutica que comprenda CCI-779 como ingrediente activo junto con 0.01% a 1% p/p de un antioxidante seleccionado del grupo conformado por: ácido cítrico, d,l- α -tocoferol, BHA, BHT, monotioglicerol, ácido ascórbico y propil galato.

En consecuencia, dicha nueva reivindicación 9 resulta ser inequívocamente novedosa frente a las enseñanzas del documento **D1**, cumpliendo a cabalidad con las disposiciones de patentabilidad establecidas en el Artículo 16 de la Decisión 486 de 2000.

6. ANÁLISIS DEL NIVEL INVENTIVO

De otro lado, el señor Examinador también ha objetado el nivel inventivo de la presente solicitud basándose en las enseñanzas de los siguientes documentos:

- US 2002/0091137 (**D1**)
- US 5362718 (**D2**)

En este sentido, el señor Examinador argumenta básicamente que la única diferencia con el documento **D1** es que las composiciones de la solicitud en cuestión poseen antioxidantes, lo que sin embargo no les concede alguna ventaja técnica debido a que en el estado del arte ya eran conocidas las composiciones de CCI-779 obtenidas mediante procesos de granulación húmeda, seca o mediante compresión directa.

Adicionalmente, el señor Examinador argumenta que la adición de antioxidantes es una práctica común en el diseño de formulaciones, de forma que un experto en la materia podría llegar fácilmente a las composiciones orales reivindicadas, mediante la realización de variaciones a los componentes sugeridos en el arte previo o ensayando diferentes mezclas.

En vista de lo anterior y con el ánimo de demostrar el inequívoco carácter inventivo que presenta la información técnica revelada en la solicitud de patente en cuestión frente a las enseñanzas de los documentos **D1** y **D2**, a continuación me permito realizar un análisis comparativo detallado entre las enseñanzas de tales anterioridades y la materia revelada en la presente solicitud de patente.

6.1 CONSIDERACIONES RESPECTO AL DOCUMENTO US 2002/0091137 (D1)

Tal como se mencionó anteriormente en el presente memorial, el documento **D1** enseña de manera general que las formulaciones de CCI-779 pueden ser obtenidas mediante compresión convencional, granulación húmeda ó granulación seca, y que dichas formulaciones pueden incluir agentes diluentes, enlazantes, lubricantes, desintegrantes, modificadores de superficie (incluyendo surfactantes), suspensores y estabilizantes farmacéuticamente aceptables.

Sin embargo, de la atenta lectura del documento **D1** es claro que en dicha anterioridad no se tiene en cuenta el problema técnico abordado en la presente solicitud, esto es, de ninguna manera se mencionan y mucho menos se solucionan los problemas generados por la baja solubilidad en agua del compuesto CCI-779 durante la obtención de formulaciones farmacéuticas que comprendan dicho compuesto activo.

Específicamente, en **D1** no se enseña y tampoco se sugiere que una formulación granulada de CCI-779 pueda presentar una solubilidad en agua muy superior a la lograda cuando dicha formulación es obtenida, por ejemplo, mediante técnicas de compresión convencionales.

Asimismo, me permito resaltar una vez más ante ese Despacho que dentro de la amplia lista de posibles aditivos enseñada en el documento **D1** (párrafo 0038) no están incluidos los antioxidantes, y mucho menos se sugiere un antioxidante escogido entre: ácido cítrico, d,l- α -tocoferol, BHA, BHT, monotioglicerol, ácido ascórbico y propil galato.

Ahora, tal y como se menciona en la descripción de la solicitud, la formulación farmacéutica reclamada es una granulación que incluye:

(i) CCI-779, (ii) un polímero soluble en agua, (iii) un surfactante, (iv) un antioxidante y (v) un agente modificador de pH,

estableciendo que sólo la combinación específica de éstos cinco (5) componentes es la que permite obtener una formulación granulada que se caracteriza por mostrar una solubilidad en agua, y por ende, una biodisponibilidad mejorada del compuesto activo (CCI-779). Sin embargo, es claro que en el documento **D1** no se enseña y

tampoco se sugiere la combinación específica de dichos componentes dentro de una formulación farmacéutica.

Por último, teniendo en cuenta las afirmaciones del señor Examinador según las cuales:

"...además la adición de antioxidantes es una práctica común en el diseño de formulaciones; de tal forma que un experto en la materia realizando variaciones a los componentes sugeridos o ensayando posibles mezclas podría llegar a las composiciones orales reivindicadas por granulación húmeda ya enseñadas en D1 logrando así mejorar en disolución y estabilidad",

es absolutamente claro que el análisis realizado por el señor Examinador no se ha enfocado de ninguna manera en el momento en que el solicitante de la invención en cuestión planteó el objetivo de obtener nuevas formulaciones de CCI-779 con alta solubilidad y biodisponibilidad, es decir, el señor Examinador realmente no está teniendo en cuenta la imperiosa necesidad que existe de que el examen de patentabilidad que lleve a cabo lo realice haciendo el esfuerzo intelectual de colocarse en la situación afrontada por el técnico con conocimientos medios en la materia antes de que el solicitante de la presente invención diera a conocer sus sorprendentes y ventajosos hallazgos técnicos.

Como consecuencia de lo planteado previamente, me permito manifestar que la materia revelada en la solicitud de patente en cuestión presenta un evidente carácter inventivo frente a las enseñanzas del documento D1.

6.2 CONSIDERACIONES RESPECTO AL DOCUMENTO US 5362718 (D2)

Básicamente, el documento D2 hace referencia a hidroxiésteres de rapamicina, enseñando que tales compuestos actúan como agentes inmunosupresivos y anti-inflamatorios.

Adicionalmente, dicha anterioridad menciona formulaciones farmacéuticas que comprenden dichos hidroxiésteres de rapamicina junto con aditivos comunes, entre los que se cuentan lubricantes, solubilizadores, agentes suspensores y de relleno.

Ahora bien, pese a la falta de argumentos técnicos por parte del señor Examinador para demostrar la supuesta falta de altura inventiva de la presente solicitud frente al documento D2, a continuación me permito señalar lo siguiente:

- En primer lugar, resulta de gran importancia resaltar que en el Examen Preliminar Internacional realizado a la presente solicitud se estableció que en el documento D2 no se hace ninguna mención a posibles formulaciones granuladas del compuesto CCI-779.

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- Asimismo, me permito señalar que **en el documento D2 no se enseña y mucho menos de sugiere algún tipo de formulación farmacéutica que incluya el compuesto CCI-779 junto con agentes surfactantes, antioxidantes y modificadores de pH, los cuales, sin embargo, son componentes esenciales dentro de las formulaciones de la presente solicitud.**
 - Por último, considero relevante mencionar que el documento **D2 no está dirigido a** solucionar los problemas de solubilidad e inestabilidad en agua del compuesto CCI-779, de manera que las enseñanzas técnicas brindadas por dicha anterioridad **no pueden de ninguna manera sugerir a la persona medianamente versada en la materia la obtención de las formulaciones farmacéuticas de la presente solicitud y mucho menos insinuar el sorprendente aumento en solubilidad y biodisponibilidad que dichas formulaciones muestran frente a las ya conocidas en el estado de la técnica.**

Por lo tanto, atentamente me permito manifestar ante ese Despacho que la materia revelada en la solicitud de patente en cuestión también presenta un inequívoco carácter inventivo frente a las enseñanzas del documento **D2**, cumpliendo entonces a cabalidad con las disposiciones de patentabilidad establecidas en el Artículo 18 de la Decisión 486 de 2000.

7. **REPORT DE EXAMEN PRELIMINAR INTERNACIONAL**

Adicionalmente considero de gran importancia resaltar que los documentos US 2002/091137 (**D1**) y US 5362718 (**D2**) fueron citados en el Reporte del Examen Preliminar Internacional realizado a la invención en cuestión (documentos anexos al presente memorial); sin embargo, dicho examen de patentabilidad concluyó que los documentos **D1** y **D2** únicamente hacen parte del estado general del arte en cuestión, pero no resultan relevantes a la hora de analizar el nivel inventivo de la presente solicitud.

8. **CONCLUSIÓN**

De conformidad con las modificaciones realizadas en el capítulo reivindicatorio de la presente solicitud, así como teniendo en cuenta los argumentos técnicos presentados para demostrar el evidente nivel inventivo que caracteriza a la invención en cuestión frente a las enseñanzas de los documentos **D1** y **D2**, resulta completamente claro que se han superado las objeciones expuestas por el señor Examinador frente a la presente solicitud, y por tanto, dicha invención es merecedora del privilegio de patente solicitado.

9. Anexo al presente memorial me permito presentar:

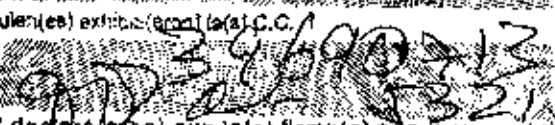
- (i) Recibo número 09 - 630 expedido por la Superintendencia de Industria y Comercio, que acredita el pago de las modificaciones mencionadas; y
- (ii) Copia del nuevo capítulo reivindicatorio compuesto por 9 reivindicaciones, el cual reemplaza al originalmente presentado y en el que se han realizado las modificaciones anteriormente mencionadas.

10. En vista de todo lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de las argumentaciones presentadas y de las modificaciones realizadas y conceder el privilegio de patente solicitado.

Señor Superintendente,


ALICIA LLOREDA RICAURTE
T.P. 53.215



NOTARIA SEXTA DE BOGOTÁ
RECONOCIMIENTO Y PRESENTACION PERSONAL
Bogotá, D.C. 08 ENE 2009
Ante mí MARÍA FERNANDA CASAS COLL,
NOTARIA SEXTA (E) DEL CÍRCULO DE
BOGOTÁ D.C.
Comparció (eron) 
Quien(es) exhibió (eron) la(s) C.C. 
Y declaró (eron) que la(s) firma(s) que aparece(n)
en el presente documento es (son) la(s) suya(s) y
que el contenido del mismo es cierto.
En constancia se firma esta diligencia


ALICIA LLOREDA RICAURTE
C.C. No. 39.690.713 de Usaquén



05-033.799

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 80017

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-033799- -00007-0000

Fecha: 2009-01-08 15:13:45 Dep: 21025 NULCRLAC/ONI
Ins: 11 PATENTE/II Lvs: 379 FAS(NACIONAL)
Act: 444 RESPULS. ARLOUL Folios: 12

RECIBO OFICIAL DE CAJA : 09 - 630
FECHA : ENERO 6 DE 2009

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO DE BOGOTA	062754387	10530601	06/01/2009	5,175,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LEHAS COMERCIALES	111,000.00
		TOTAL :	\$ 111,000.00

SON: CIENTO ONCE MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

REIVINDICACIONES

1. Una composición farmacéutica para administración oral que comprende una granulación, dicha granulación comprende CCI-779, un polímero soluble en agua, un surfactante, 0.01% a 1% p/p de un antioxidante seleccionado del grupo que consiste de: ácido cítrico, d,l- α -tocoferol, BHA, BHT, monotioglicerol, ácido ascórbico y propil galato, y un agente modificador de pH.
2. La composición de la reivindicación 1, en donde el polímero soluble en agua es PVP, hidroxipropilmetilcelulosa, polietilén glicol, una ciclodextrina o mezclas de estos.
3. La composición de la reivindicación 2, en donde el polímero soluble en agua es PVP.
4. La composición de cualquiera de las reivindicaciones 1 a 3, en donde el surfactante es polisorbato 80, lauril sulfato de sodio, dodecil sulfato de sodio, una sal de ácido biliar, un aceite vegetal etoxilado, un copolímero de bloque polioxietileno-polioxipropileno, o un poloxámero.
5. La composición de la reivindicación 4, en donde el surfactante es lauril sulfato de sodio o dodecil sulfato de sodio.
6. La composición farmacéutica de cualquiera de las reivindicaciones 1 a 5, en donde el agente modificador de pH es seleccionado del grupo consistente de citrato de sodio, ácido cítrico, ácido clorhídrico diluido y mezclas de estos.
7. Un proceso para preparar una composición oral de CCI-779, que comprende:
 - (a) disolver CCI-779 y 0.01% a 1% p/p de un antioxidante en un alcohol;
 - (b) disolver PVP, un agente modificador de pH, y un surfactante en agua;

- (c) combinar las soluciones acuosa y alcohólica para proporcionar una solución hidrohólica;
- (d) *adicionar la solución hidrohólica a una mezcla que contiene uno o más excipientes intragranulares;*
- (e) granular la mezcla; y
- (f) *secar la granulación resultante.*

8. Un proceso para preparar una composición oral de CCI-779, que comprende:

- (a) disolver CCI-779 y 0.01% a 1% p/p de un antioxidante en un alcohol;
- (b) disolver PVP, un agente modificador de pH, y un surfactante en agua;
- (c) adicionar las soluciones acuosa y alcohólica por pasos, y en una o más porciones de cada una, a una mezcla que contiene uno o más excipientes intragranulares;
- (e) granular la mezcla; y
- (f) secar la granulación resultante.

9. Una composición oral de CCI-779 de conformidad con la reivindicación 1, preparada por granulación en húmedo.



US 20020091137A1

(19) **United States**(12) **Patent Application Publication** (10) Pub. No.: **US 2002/0091137 A1**
Dukart et al. (43) Pub. Date: **Jul. 11, 2002**(54) **USE OF CCI-779 AS AN ANTINEOPLASTIC AGENT**(21) Appl. No.: **10/010,584**(22) Filed: **Nov. 13, 2001**(75) Inventors: **Gary Dukart, Ambler, PA (US); James J. Gibbons JR., Westwood, NJ (US); Lisa A. Spulcher, Havertown, PA (US); Philip Frust, Morris Township, NJ (US); Carolyn M. Discasanti-Marro, Cortlandt Manor, NY (US)****Related U.S. Application Data**

(63) Non-provisional of provisional application No. 60/249,077, filed on Nov. 15, 2000.

Publication Classification(51) Int. Cl.⁷ **A61K 31/47**(52) U.S. Cl. **514/310****Correspondence Address:****Arnold S. Mhowsky
American Home Products Corporation
Patent Law Department - 2B
Five Giralda Farms
Madison, NJ 07940 (US)**(57) **ABSTRACT**(73) Assignee: **American Home Products Corporation, Madison, NJ**This invention provides the use of **CCI-779** in the treatment of neoplasms.

USE OF CCI-779 AS AN ANTINEOPLASTIC AGENT

BACKGROUND OF THE INVENTION

[0001] This application claims priority from copending provisional application Serial No. 60/249,077, filed Nov. 15, 2000, the entire disclosure of which is hereby incorporated by reference.

[0002] This invention relates to the use of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) as an antineoplastic agent.

[0003] Rapamycin is a macrocyclic tricyclic antibiotic produced by *Streptomyces hygroscopicus*, which was found to have antifungal activity, particularly against *Candida albicans*, both in vitro and in vivo [C. Vezina et al., J. Antibiot. 28, 721 (1975); S. N. Sehgal et al., J. Antibiot. 28, 727 (1975); H. A. Baker et al., J. Antibiot. 31, 539 (1978); U.S. Pat. No. 3,929,992; and U.S. Pat. No. 3,993,749]. Additionally, rapamycin alone (U.S. Pat. No. 4,885,171) or in combination with plicic acid (U.S. Pat. No. 4,401,653) has been shown to have antitumor activity.

[0004] The immunosuppressive effects of rapamycin have been disclosed in FASEB J. 3, 3411 (1989). Cyclosporin A and FK-506, other macrocyclic molecules, also have been shown to be effective as immunosuppressive agents, therefore useful in preventing transplant rejection [FASEB J. 3, 3411 (1989); FASEB J. 3, 5256 (1989); R. Y. Calne et al., Lancet 1183 (1978); and U.S. Pat. No. 5,100,899]. R. Martel et al. [Can. J. Physiol. Pharmacol. 55, 48 (1977)] disclosed that rapamycin is effective in the experimental allergic encephalomyelitis model, a model for multiple sclerosis; in the adjuvant arthritis model, a model for rheumatoid arthritis; and effectively inhibited the formation of IgE-like antibodies.

[0005] Rapamycin is also useful in preventing or treating systemic lupus erythematosus [U.S. Pat. No. 5,078,999], pulmonary inflammation [U.S. Pat. No. 5,080,899], insulin dependent diabetes mellitus [U.S. Pat. No. 5,321,009], skin disorders, such as psoriasis [U.S. Pat. No. 5,286,730], bowel disorders [U.S. Pat. No. 5,286,731], smooth muscle cell proliferation and intimal thickening following vascular injury [U.S. Pat. Nos. 5,288,711 and 5,516,781], adult T-cell leukemia/lymphoma [European Patent Application 525,960 A1], ocular inflammation [U.S. Pat. No. 5,387,589], malignant carcinomas [U.S. Pat. No. 5,206,018], cardiac inflammatory disease [U.S. Pat. No. 5,496,832], and anemia [U.S. Pat. No. 5,561,138].

[0006] The preparation and use of hydroxyesters of rapamycin, including CCI-779, are disclosed in U.S. Pat. No. 5,362,718.

DESCRIPTION OF THE INVENTION

[0007] This invention provides the use of CCI-779 as an antineoplastic agent, and particularly for neoplasms which are refractory to standard therapy, or for whom standard therapy is not appropriate. In particular CCI-779 is useful in the treatment of renal cancer, soft tissue cancer, breast cancer, neuroendocrine tumor of the lung, cervical cancer, uterine cancer, head and neck cancer, glioblastoma, non-small lung cell cancer, prostate cancer, pancreatic cancer, lymphoma, melanoma, small cell lung cancer, ovarian cancer, endometrial cancer, and colon cancer.

[0008] As used in accordance with this invention, the term "treatment" means treating a mammal having a neoplastic disease by providing said mammal an effective amount of CCI-779 with the purpose of inhibiting growth of the neoplasm in such mammal, eradication of the neoplasm, or palliation of the neoplasm.

[0009] As used in accordance with this invention, the term "providing," with respect to providing CCI-779, means either directly administering CCI-779, or administering a prodrug, derivative, or analog which will form an effective amount of CCI-779 within the body.

[0010] As used in accordance with this invention, the term "refractory neoplasm" refers to neoplasms in patients which typically had progressed following treatment with standard chemotherapy that was appropriate for that given neoplasm.

[0011] The preparation of CCI-779 is described in U.S. Pat. No. 5,362,718, which is hereby incorporated by reference.

[0012] The antineoplastic activity of CCI-779 was confirmed in a preclinical in vitro and in vivo standard pharmacological test procedure which measured the ability of CCI-779 to treat human renal cell cancer (a rapidly progressive disease with very limited treatment options), as well as in two Phase I human clinical trials. The procedures used and results obtained are briefly described below.

PRECLINICAL TEST PROCEDURES

[0013] In vitro test procedure: Renal tumor lines HTB-44 and CRL-1161 were obtained from the American Tissue Culture Collection (ATCC), Bethesda, Md. SN12-C line was obtained from Dr. J. Fidler, M.D. Anderson Hospital, Houston, Tex. Cells were plated in MEM (Gibco) supplemented with 2 mM glutamine, 1 mM sodium pyruvate, 5 ml penicillin-streptomycin solution, 1 mM non-essential amino acid solution, 10% fetal bovine solution. Cells (5×10^3) were plated in 96 well plates with a final volume of 200 μ l and incubated for 24 hours at 37° C. Log dilutions of CCI-779 beginning at 100 μ g/ml were then added to the cultures for 48 hours. Over the last 5 hours, cells were pulsed with 1 μ Ci ^{3} H-thymidine (New England Nuclear, 6.7 Ci/mMol). Cells were then harvested and the degree of thymidine uptake determined by liquid scintillation spectrometry. The IC₅₀ was determined as the concentration that produced 50% of the maximum uptake of thymidine in control untreated cells.

[0014] In vivo test procedure: Female Balb/c nude mice were obtained from Charles River Labs, Wilmington, Del., at 6-8 weeks of age. Mice (n=10/group) were injected sc with 5×10^6 cells resuspended in a 50% solution of Matrigel (BD Biosciences) and tumors allowed to develop. When tumor size reached 100 mg, mice were treated orally with CCI-779 at 25 mg/kg. CCI-779 was dosed for 5 consecutive days with repeated 14 day cycles throughout the duration of the experiment. The formulation used for CCI-779 was a 50% ethanol, 49% phosal, 1% tween 80 vehicle for resuspending CCI-779, where the stock was resuspended into a 1:10 dilution of the vehicle prior to dosing. Tumor growth was evaluated using a vernier caliper and volume ($l \times w \times h$) was converted to mass using the formula: $1 \text{ cm}^3/2$.

[0015] Results:

[0016] Human renal cell tumors were cultured in vitro in the presence or absence of CCI-779 for 3 days and the effect

on growth determined by ^3H -thymidine incorporation of control versus treated cells. Table 1 shows that IC_{50} (50% growth inhibitory concentration) for all 3 lines tested was in the low nM range.

TABLE 1

The effect of CCI-779 on the growth of human renal tumor cells *in vitro*

Renal Tumor Line	CCI-779 IC_{50} (nM)
HTB-44	5.0
CRL-1161	2.5
SN12-C	5.5

[0017] The effect of CCI-779 in two human renal lines (HTB-44 and CRL-1161) were evaluated *in vivo* by engrafting tumor cells on the flanks of nude mice. Once tumors were established at a size of about 100 mg, mice were treated with CCI-779 or a vehicle control. Treatment with CCI-779 at 25 mg/kg resulted in significant inhibition of tumor cell growth in the mice (Table 2).

[0018] Table 2 Effect of CCI-779 on the growth of human renal tumor cells in nude mouse xenografts

TABLE 2

Effect of CCI-779 on the growth of human renal tumor cells in nude mouse xenografts

Cell Line	Drug	Tumor Mass (mg)					
		0	7	14	21	28	35
HTB-44	Control	288 $\pm$ 27	219 $\pm$ 18	616 $\pm$ 55	1095 $\pm$ 44	2023 $\pm$ 247	2412 $\pm$ 342
	CCI	290 $\pm$ 15	156 $\pm$ 13*	352 $\pm$ 48*	451 $\pm$ 85*	920 $\pm$ 155*	1050 $\pm$ 193*
	% TC	100	71	41	41	48	44
CRL-1161	Control	273 $\pm$ 18	355 $\pm$ 36	413 $\pm$ 60	480 $\pm$ 127	545 $\pm$ 170	507 $\pm$ 156
	CCI	272 $\pm$ 14	219 $\pm$ 16*	326 $\pm$ 17*	200 $\pm$ 21*	229 $\pm$ 28*	269 $\pm$ 30
	% TC	100	62	63	42	42	53

*p value = <0.05

% TC = Treated/Control $\times$ 100

[0019] Clinical Trial:

[0020] Two single agent (CCI-779) Phase I clinical trials have been conducted. In the first study, CCI-779 was administered as a 30 minute i.v. infusion daily for 5 days, every two to three weeks. In the second study, CCI-779 was administered as a 30 minute i.v. infusion, once weekly. Both trials were open label, ascending dose, single-arm, multi-center studies. Patients were allowed to continue treatment as long as the CCI-779 was tolerated and there was no evidence of obvious disease progression. The following eligibility criteria were used:

[0021] Inclusion Criteria

[0022] 1. Patients with a histologic diagnosis of advanced cancer (solid tumors and, in the first study, lymphomas) who are refractory to standard therapy or for whom standard therapy is not appropriate.

[0023] 2. Measurable or evaluable disease.

[0024] 3. At least 3 weeks since prior chemotherapy and/or radiation therapy (6 weeks since nitrosoureas or mitomycin C).

[0025] 4. At least 4 weeks since any other investigational agent.

[0026] 5. Age at least 18 years old.

[0027] 6. Adequate bone marrow, renal, and hepatic function.

[0028] 7. Serum cholesterol $\leq$ 350 mg/dL and triglycerides $\leq$ 300 mg/dL.

[0029] 8. ECOG performance status 0-2.

[0030] 9. Life expectancy of at least 3 months.

[0031] 10. Signed, dated, witnessed written informed consent.

[0032] A total of 63 patients and 24 patients were enrolled in first and second studies, respectively. Dose levels ranged from 0.75-24 mg/m² and 7.5-220 mg/m², with the daily $\times$ 5 every 2 weeks and weekly schedules, respectively.

[0033] The following summarizes the results that were obtained:

[0034] In patients having renal cancer on the weekly schedule, 1 partial response ($\geq$ 50% reduction in tumor size)

and 2 minor responses ($\geq$ 25% but <50% reduction in tumor size) were observed. In renal cancer patients on the daily $\times$ 5 schedule, 1 minor response, 1 unconfirmed minor response, and 1 stable disease (<25% increase to <25% reduction in tumor size) lasting approximately 5 months were observed. In patients having soft tissue sarcoma on the daily $\times$ 5 dosage schedule, 1 possible partial response, 2 minor responses, and 1 stable disease lasting approximately 5 months were observed. In patients with breast cancer on the weekly dosage schedule, one partial response was observed. In patients with neuroendocrine tumor of the lung on the weekly dosage schedule, one partial response was observed. In patients having cervical cancer on the daily $\times$ 5 dosage schedule, one minor response was observed. In patients having uterine cancer receiving the daily $\times$ 5 dosage schedule, one unconfirmed minor response was observed. In patients having head and neck cancer receiving the daily $\times$ 5 dosage schedule, 1 stable disease for approximately 8 months was observed. In patients having non-small cell lung cancer receiving the daily $\times$ 5 dosage schedule, one partial response was observed. These results are particularly surprising, considering that the patients in these studies had advanced cancers that were generally refractory to standard

treatment, and also considering that these were Phase I clinical trials, in which efficacy is often limited, as the primary objective of a Phase I trial is to determine the safety and tolerability of the drug being evaluated.

[0035] Based on the results of the preclinical and clinical test procedures, CCI-779 is useful in treating neoplasms, in particular, refractory neoplasms. More particularly, CCI-779 is useful in treating treatment of renal carcinoma, soft tissue carcinoma, breast cancer, neuroendocrine tumor of the lung, cervical cancer, uterine cancer, head and neck cancer, glioblastoma, non-small cell lung cancer, prostate cancer, pancreatic cancer, lymphoma, melanoma, small cell lung cancer, ovarian cancer, endometrial cancer, and colon cancer.

[0036] As typical with chemotherapy, dosage regimens are closely monitored by the treating physician, based on numerous factors including the severity of the disease, response to the disease, any treatment related toxicities, age, and health of the patient. Based on the results obtained with CCI-779, it is projected that initial i.v. infusion dosages will be between about 0.1 and 100 mg/m² when administered on a daily dosage regimen, and between about 1 and 1000 mg/m² when administered on a weekly dosage regimen. Other dosage regimens and variations are foreseeable, and will be determined through physician guidance. It is preferred that CCI-779 is administered by i.v. infusion or orally, preferably in the form of tablets or capsules. Other routes of administration are also feasible, such as via implants, parenterally (besides i.v., such as intraperitoneal and subcutaneous injections), rectally, intranasally, vaginally, and transdermally.

[0037] Dosage regimens are expected to vary according to the route of administration. For example, dosages for oral administration are often up to tenfold greater than for i.v. administration. It is anticipated that CCI-779 may be administered as the sole active chemotherapeutic agent, or may be part of a chemotherapeutic regimen containing more than one antineoplastic agent. The use of concomitant chemotherapeutic agents often allows for dosage reduction of each particular agent, thereby increasing the safety margin of the particular agents.

[0038] Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g., corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses; flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginate acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, inulin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Preferred surface

modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearyl alcohol, octonactopul emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). The oral formulation may also consist of administering the active ingredient in water or a fruit juice, containing appropriate solubilizers or emulsifiers as needed.

[0039] In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

[0040] The compounds of this invention may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmaceutically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propyl-cellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0041] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

[0042] For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

[0043] Transdermal administration may be accomplished through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is not toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

[0044] Suppository formulations may be made from traditional materials, including cocoa butter, with or without

the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

What is claimed is:

1. A method of treating a neoplasm in a mammal in need thereof, which comprises providing to said mammal an effective amount of CCI-779.

2. A method of treating a refractory neoplasm in a mammal in need thereof, which comprises providing to said mammal an effective amount of CCI-779.

3. The method according to claim 1, wherein the neoplasm is renal cancer.

4. The method according to claim 1, wherein the neoplasm is soft tissue sarcoma.

5. The method according to claim 1, wherein the neoplasm is breast cancer.

6. The method according to claim 1, wherein the neoplasm is a neuroendocrine tumor of the lung.

7. The method according to claim 1, wherein the neoplasm is cervical cancer.

8. The method according to claim 1, wherein the neoplasm is uterine cancer.

9. The method according to claim 1, wherein the neoplasm is a head and neck cancer.

10. The method according to claim 1, wherein the neoplasm is glioblastoma.

11. The method according to claim 1, wherein the neoplasm is non-small cell lung cancer.

12. The method according to claim 1, wherein the neoplasm is prostate cancer.

13. The method according to claim 1, wherein the neoplasm is pancreatic cancer.

14. The method according to claim 1, wherein the neoplasm is lymphoma.

15. The method according to claim 1, wherein the neoplasm is melanoma.

16. The method according to claim 1, wherein the neoplasm is small cell lung cancer.

17. The method according to claim 1, wherein the neoplasm is ovarian cancer.

18. The method according to claim 1, wherein the neoplasm is colon cancer.

19. The method according to claim 1, wherein the neoplasm is endometrial cancer.

* * * * *

United States Patent [19]
Skotnicki et al.

US005362718A

[11] **Patent Number:** **5,362,718**
 [43] **Date of Patent:** **Nov. 8, 1994**

[54] **RAPAMYCIN HYDROXYESTERS**

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[21] **Appl. No.:** **229,261**

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C07D 498/16; C07D 7/04

[52] **U.S. Cl.:** **514/63; 514/291;**
540/452; 540/456

[58] **Field of Search:** **540/456, 452; 514/291,**
514/63

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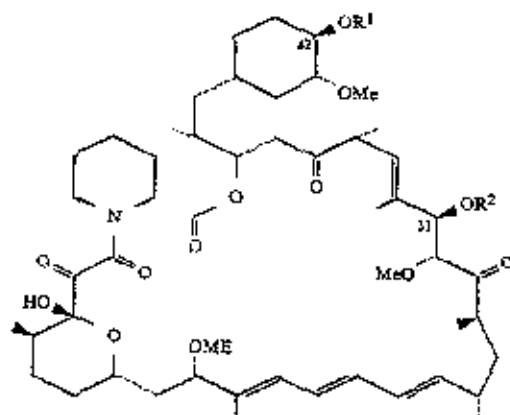
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Primary Examiner—Robert T. Bond
Attorney, Agent, or Firm—Arnold S. Milowsky

[57] **ABSTRACT**

A compound of the structure

(Abstract continued on next page.)



wherein R^1 and R^2 are each, independently, hydrogen or $-\text{CO}(\text{CR}^3\text{R}^4)_b(\text{CR}^5\text{R}^6)_d\text{CR}^7\text{R}^8\text{R}^9$; R^3 and R^4 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, trifluoromethyl, or $-\text{F}$; R^5 and R^6 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, $-(\text{CR}^3\text{R}^4)_f\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$, or R^5 and R^6 may be taken together to form X or a cycloalkyl ring that is optionally mono-, di-, or tri-substituted with $-(\text{CR}^3\text{R}^4)_f\text{OR}^{10}$;

R^7 is hydrogen, alkyl, alkenyl, alkynyl, $-(\text{CR}^3\text{R}^4)_f\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$;

R^8 and R^9 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, $-(\text{CR}^3\text{R}^4)_f\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$, or R^8 and R^9 may be taken together to form X or a cycloalkyl ring that is optionally mono-, di-, or tri-substituted with $-(\text{CR}^3\text{R}^4)_f\text{OR}^{10}$;

R^{10} is hydrogen, alkyl, alkenyl, alkynyl, tri-(alkyl)silyl, tri-(alkyl)silylethyl, triphenylmethyl, benzyl, alkoxymethyl, tri-(alkyl)silylethoxymethyl, chloroethyl, or tetrahydropyranyl;

R^{11} is hydrogen, alkyl, alkenyl, alkynyl, or phenylalkyl;

X is 5-(2,2-dialkyl)[1,3]dioxanyl, 5-(2,2-dicycloalkyl)[1,3]dioxanyl, 4-(2,2-dialkyl)[1,3]dioxanyl, 4-(2,2-dicycloalkyl)[1,3]dioxanyl, 4-(2,2-dialkyl)[1,3-dioxalanyl, or 4-(2,2-dicycloalkyl)[1,3]dioxalanyl;

$b=0-6$;

$d=0-6$; and

$f=0-6$

with the proviso that R^1 and R^2 are both not hydrogen and further provided that either R^1 or R^2 contains at least one $-(\text{CR}^3\text{R}^4)_f\text{OR}^{10}$, X, or $-(\text{CR}^3\text{R}^4)_f\text{OR}^{10}$ substituted cycloalkyl group, or a pharmaceutically acceptable salt thereof which is useful as an immunosuppressive, antiinflammatory, antifungal, antiproliferative, and antitumor agent.

24 Claims, No Drawings

RAPAMYCIN HYDROXYESTERS

BACKGROUND OF THE INVENTION

This invention relates to hydroxyesters of rapamycin and a method for using them for inducing immunosuppression, and in the treatment of transplantation rejection, graft vs. host disease, autoimmune diseases, diseases of inflammation, adult T-cell leukemia/lymphoma, solid tumors, fungal infections, and hyperproliferative vascular disorders.

Rapamycin is a macrocyclic triene antibiotic produced by *Streptomyces hygroscopicus*, which was found to have antifungal activity, particularly against *Candida albicans*, both *in vitro* and *in vivo* [C. Vezina et al., J. Antibiot. 28, 721 (1975); S. N. Sehgal et al., J. Antibiot. 28, 727 (1975); H. A. Baker et al., J. Antibiot. 31, 539 (1978); U.S. Pat. Nos. 3,929,992; and 3,993,749].

Rapamycin alone (U.S. Pat. No. 4,885,171) or in combination with picibanil (U.S. Pat. No. 4,401,653) has been shown to have antitumor activity. R. Martel et al. [Can. J. Physiol. Pharmacol. 55, 48 (1977)] disclosed that rapamycin is effective in the experimental allergic encephalomyelitis model, a model for multiple sclerosis; in the adjuvant arthritis model, a model for rheumatoid arthritis; and effectively inhibited the formation of IgE-like antibodies.

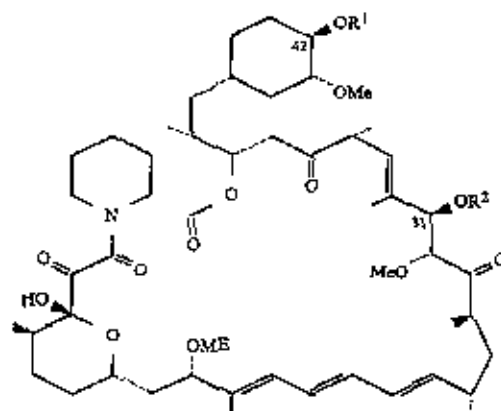
The immunosuppressive effects of rapamycin have been disclosed in FASEB 3, 3411 (1989). Cyclosporin A and FK-506, other macrocyclic molecules, also have been shown to be effective as immunosuppressive agents, therefore useful in preventing transplant rejection [FASEB 3, 3411 (1989); FASEB 3, 5256 (1989); R. Y. Caine et al., Lancet 1183 (1978); and U.S. Pat. No. 5,100,899].

Rapamycin has also been shown to be useful in preventing or treating systemic lupus erythematosus [U.S. Pat. No. 5,078,999], pulmonary inflammation [U.S. Pat. No. 5,080,899], insulin dependent diabetes mellitus [Fifth Int. Conf. Inflamma. Res. Assoc. 121 (Abstract) (1990)], smooth muscle cell proliferation and intimal thickening following vascular injury [Morris, R. J. Heart Lung Transplant 11 (pt. 2): 197 (1992)], adult T-cell leukemia/lymphoma [European Patent Application 525,960 A1], and ocular inflammation [European Patent Application 532,862 A1].

Mono- and diacylated derivatives of rapamycin (esterified at the 28 and 43 positions) have been shown to be useful as antifungal agents (U.S. Pat. No. 4,316,885) and used to make water soluble aminoacyl prodrugs of rapamycin (U.S. Pat. No. 4,650,803). Recently, the numbering convention for rapamycin has been changed; therefore according to Chemical Abstracts nomenclature, the esters described above would be at the 31- and 42- positions.

DESCRIPTION OF THE INVENTION

This invention provides derivatives of rapamycin which are useful as immunosuppressive, antiinflammatory, antifungal, antiproliferative, and antitumor agents having the structure



wherein R^1 and R^2 are each, independently, hydrogen or $-\text{CO}(\text{CR}^3\text{R}^4)_b(\text{CR}^5\text{R}^6)_c\text{CR}^7\text{R}^8\text{R}^9$;

R^3 and R^4 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, trifluoromethyl, or $-\text{F}$;

R^5 and R^6 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, $-(\text{CR}^3\text{R}^4)_d\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$, or R^5 and R^6 may be taken together to form X or a cycloalkyl ring of 3-8 carbon atoms that is optionally mono-, di-, or tri-substituted with $-(\text{CR}^3\text{R}^4)_e\text{OR}^{10}$;

R^7 is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, $-(\text{CR}^3\text{R}^4)_f\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$;

R^8 and R^9 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, $-(\text{CR}^3\text{R}^4)_g\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$, or R^8 and R^9 may be taken together to form X or a cycloalkyl ring of 3-8 carbon atoms that is optionally mono-, di-, or tri-substituted with $-(\text{CR}^3\text{R}^4)_h\text{OR}^{10}$;

R^{10} is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, tri-(alkyl of 1-6 carbon atoms)silyl, tri-(alkyl of 1-6 carbon atoms)silylethyl, triphenylmethyl, benzyl, alkoxymethyl of 2-7 carbon atoms, tri-(alkyl of 1-6 carbon atoms)silylethoxymethyl, chloroethyl, or tetrahydropyranyl;

R^{11} is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, or phenylalkyl of 7-10 carbon atoms;

X is 5-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxanyl, 5-(2,2-di-(cycloalkyl of 3-8 carbon atoms))[1,3]dioxanyl, 4-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxanyl, 4-(2,2-di-(cycloalkyl of 3-8 carbon atoms))[1,3]dioxanyl, 4-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxalanyl, or 4-(2,2-di-(cycloalkyl of 3-8 carbon atoms))[1,3]dioxalanyl;

$b=0-6$;

$d=0-6$; and

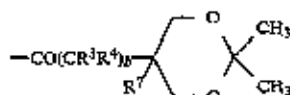
$f=0-6$

with the proviso that R^1 and R^2 are both not hydrogen and further provided that either R^1 or R^2 contains at least one $-(\text{CR}^3\text{R}^4)_e\text{OR}^{10}$, X, or $-(\text{CR}^3\text{R}^4)_e\text{OR}^{10}$ substituted cycloalkyl of 3-8 carbon atoms group, or a pharmaceutically acceptable salt thereof.

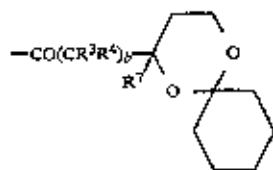
The pharmaceutically acceptable salts are those derived from such inorganic cations such as sodium, potassium, and the like; and organic bases such as: mono-, di-, and trialkyl amines of 1-6 carbon atoms, per alkyl group and mono-, di-, and trihydroxyalkyl amines of 1-6 carbon atoms per alkyl group, and the like.

The terms alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, and alkynyl of 2-7 carbon atoms, include both straight chain as well as branched carbon chains. As the compounds of this invention can contain more than one $-(CR^3R^4)OR^{10}$ group, R^3 , R^4 , f , and R^{10} can be the same or different. Similarly, when other generic substituent descriptions are repeated in the same structure, they can be the same or different.

For a compound in which R^1 contains R^8 and R^9 taken together to form X, where X is 5-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxanyl, the alkyl group of X contains 1 carbon atom, and $d=0$, R^1 would have the following structure.



Similarly, for a compound in which R^1 contains R^8 and R^9 taken together to form X, where X is 4-(2,2-di-(cycloalkyl of 3-8 carbon atoms))[1,3]dioxanyl, the cycloalkyl group of X contains 6 carbon atom, and $d=0$, R^1 would have the following structure.



For compounds containing X, preferred compounds include those in which the alkyl group of X, if present, is methyl and the cycloalkyl group of X, if present, is cyclohexyl.

When R^{10} is not hydrogen, alkyl, alkenyl, or alkynyl, it is intended that R^{10} is a group that can serve as an alcohol protecting group. Thus, these groups are intermediates of free hydroxylated compounds, as well as being biologically active in their own right. R^{10} covers tri-(alkyl of 1-6 carbon atoms)silyl, tri-(alkyl of 1-6 carbon atoms)silyl, triphenylmethyl, benzyl, alkoxymethyl of 2-7 carbon atoms, tri-(alkyl of 1-6 carbon atoms)silylethoxymethyl, chloroethyl, and tetrahydropyranyl groups. Other alcohol protecting groups are known by one skilled in the art and are also considered part of this invention.

Of the compounds of this invention preferred members are those in which R^2 is hydrogen; those in which R^2 is hydrogen, $b=0$, and $d=0$; those in which R^2 is hydrogen, $b=0$, $d=0$, and R^8 and R^9 are each, independently hydrogen, alkyl, or $-(CR^3R^4)OR^{10}$, or are taken together to form X.

Compounds of this invention having the ester group $-CO(CR^3R^4)OR^{10}$ at the 42- or 31,42-positions can be prepared by acylation of rapamycin using protected hydroxy and polyhydroxy acids, alkoxo or polyalkoxo carboxylic acids that have been activated, followed by removal of the alcohol protecting

groups, if so desired. Several procedures for carboxylate activation are known in the art, but the preferred methods utilize carbodiimides, mixed anhydrides, or acid chlorides. For example, an appropriately substituted carboxylic acid can be activated as a mixed anhydride, with an acylating group such as 2,4,6-trichlorobenzoyl chloride. Treatment of rapamycin with the mixed anhydride under mildly basic condition provides the desired compounds. Alternatively, the acylation reaction can be accomplished with 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride and dimethylaminopyridine. Mixtures of 42- and 31,42-esters can be separated by chromatography.

The 31-ester-42-hydroxy compounds of this invention can be prepared by protecting the 42-alcohol of rapamycin with a protecting group, such as with a tert-butyl dimethylsilyl group, followed by esterification of the 31-position by the procedures described above. The preparation of rapamycin 42-silyl ethers is described in U.S. Pat. No. B1 5,120,842, which is hereby incorporated by reference. Removal of the protecting group provides the 31-esterified compounds. In the case of the tert-butyl dimethylsilyl protecting group, deprotection can be accomplished under mildly acidic conditions, such as acetic acid/water/THF. The deprotection procedure is described in Example 15 of U.S. Pat. No. 5,118,678, which is hereby incorporated by reference.

Having the 31-position esterified and the 42-position deprotected, the 42-position can be esterified using a different acylating agent than was reacted with the 31-alcohol, to give compounds having different esters at the 31- and 42-positions. Alternatively, the 42-esterified compounds, prepared as described above, can be reacted with a different acylating agent to provide compounds having different esters at the 31- and 42-positions.

This invention also covers analogous hydroxy esters of other rapamycins such as, but not limited to, 29-demethoxyrapamycin, [U.S. Pat. No. 4,375,464, 32-demethoxyrapamycin under C.A. nomenclature]; rapamycin derivatives in which the double bonds in the 1-, 3-, and/or 5-positions have been reduced [U.S. Pat. No. 5,023,262]; 29-desmethylrapamycin [U.S. Pat. No. 5,093,339, 32-desmethylrapamycin under C.A. nomenclature]; 7,29-bisdesmethylrapamycin [U.S. Pat. No. 5,093,338, 7,32-desmethylrapamycin under C.A. nomenclature]; and 15-hydroxyrapamycin [U.S. Pat. No. 5,102,876]. The disclosures in the above cited U.S. Patents are hereby incorporated by reference.

Immunosuppressive activity for representative compounds of this invention was evaluated in an in vitro standard pharmacological test procedure to measure the inhibition of lymphocyte proliferation (LAF) and in two in vivo standard pharmacological test procedures. The pinch skin graft test procedure measures the immunosuppressive activity of the compound tested as well as the ability of the compound tested to inhibit or treat transplant rejection. The adjuvant arthritis standard pharmacological test procedure, which measures the ability of the compound tested to inhibit immune mediated inflammation. The adjuvant arthritis test procedure is a standard pharmacological test procedure for rheumatoid arthritis. The procedures for these standard pharmacological test procedures are provided below.

The mitogen-induced thymocyte proliferation procedure (LAF) was used as an in vitro measure of the immunosuppressive effects of representative com-

pounds. Briefly, cells from the thymus of normal BALB/c mice are cultured for 72 hours with PHA and IL-1 and pulsed with tritiated thymidine during the last six hours. Cells are cultured with and without various concentrations of rapamycin, cyclosporin A, or test compound. Cells are harvested and incorporated radioactivity is determined. Inhibition of lymphoproliferation is assessed as percent change in counts per minute from nondrug treated controls. For each compound evaluated, rapamycin was also evaluated for the purpose of comparison. An IC_{50} was obtained for each test compound as well as for rapamycin. When evaluated as a comparator for the representative compounds of this invention, rapamycin had an IC_{50} ranging from 0.6-1.3 nM. The results obtained are provided as an IC_{50} and as the percent inhibition of T-cell proliferation at 0.1 μ M. The results obtained for the representative compounds of this invention were also expressed as a ratio compared with rapamycin. A positive ratio indicates immunosuppressive activity. A ratio of greater than 1 indicates that the test compound inhibited thymocyte proliferation to a greater extent than rapamycin. Calculation of the ratio is shown below.

$$\frac{IC_{50} \text{ of Rapamycin}}{IC_{50} \text{ of Test Compound}}$$

Representative compounds of this invention were also evaluated in an in vivo test procedure designed to determine the survival time of pinch skin graft from male BALB/c donors transplanted to male C57BL/2K recipients. The method is adapted from Billingham R. E. and Medawar P. B., J. Exp. Biol. 28:385-402, (1951). Briefly, a pinch skin graft from the donor was grafted on the dorsum of the recipient as a allograft, and an isograft was used as control in the same region. The recipients were treated with either varying concentrations of test compounds intraperitoneally or orally. Rapamycin was used as a test control. Untreated recipients serve as rejection control. The graft was monitored daily and observations were recorded until the graft became dry and formed a blackened scab. This was considered as the rejection day. The mean graft survival time (number of days $\pm$ S.D.) of the drug treatment group was compared with the control group. The following table shows the results that were obtained. Results are expressed as the mean survival time in days. Untreated (control) pinch skin grafts are usually rejected within 6-7 days. Compounds were tested using a dose of 4 mg/kg.

The adjuvant arthritis standard pharmacological test procedure measures the ability of test compounds to prevent immune mediated inflammation and inhibit or treat rheumatoid arthritis. The following briefly describes the test procedure used. A group of rats (male inbred Wistar Lewis rats) are pre-treated with the compound to be tested (1 h prior to antigen) and then injected with Freud's Complete Adjuvant (FCA) in the right hind paw to induce arthritis. The rats are then orally dosed on a Monday, Wednesday, Friday schedule from day 0-14 for a total of 7 doses. Both hind paws are measured on days 16, 23, and 30. The difference in paw volume (mL) from day 16 to day 0 is determined and a percent change from control is obtained. The left hind paw (uninjected paw) inflammation is caused by T-cell mediated inflammation and is recorded in the above table (% change from control). The right hind paw inflammation, on the other hand, is caused by non-

specific inflammation. Compounds were tested at a dose of 5 mg/kg. The results are expressed as the percent change in the uninjected paw at day 16 versus control; the more negative the percent change, the more potent the compound. Rapamycin provided between -70% and -90% change versus control, indicating that rapamycin treated rats had between 70-90% less immune induced inflammation than control rats.

The results obtained in these standard pharmacological test procedures are provided following the procedure for making the specific compounds that were tested.

The results of these standard pharmacological test procedures demonstrate immunosuppressive activity both in vitro and in vivo for the compounds of this invention. The results obtained in the LAF test procedure indicates suppression of T-cell proliferation, thereby demonstrating the immunosuppressive activity of the compounds of this invention. Further demonstration of the utility of the compounds of this invention as immunosuppressive agents was shown by the results obtained in the skin graft and adjuvant arthritis standard pharmacological test procedures. Additionally, the results obtained in the skin graft test procedure further demonstrates the ability of the compounds of this invention to treat or inhibit transplantation rejection. The results obtained in the adjuvant arthritis standard pharmacological test procedure further demonstrate the ability of the compounds of this invention to treat or inhibit rheumatoid arthritis.

Based on the results of these standard pharmacological test procedures, the compounds are useful in the treatment or inhibition of transplantation rejection such as kidney, heart, liver, lung, bone marrow, pancreas (islet cells), cornea, small bowel, and skin allografts, and heart valve xenografts; in the treatment or inhibition of autoimmune diseases such as lupus, rheumatoid arthritis, diabetes mellitus, myasthenia gravis, and multiple sclerosis; and diseases of inflammation such as psoriasis, dermatitis, eczema, seborrhea, inflammatory bowel disease, pulmonary inflammation (including asthma, chronic obstructive pulmonary disease, emphysema, acute respiratory distress syndrome, bronchitis, and the like), and eye uveitis.

Because of the activity profile obtained, the compounds of this invention also are considered to have antitumor, antifungal activities, and antiproliferative activities. The compounds of this invention therefore also useful in treating solid tumors, adult T-cell leukemia/lymphoma, fungal infections, and hyperproliferative vascular diseases such as restenosis and atherosclerosis. When used for restenosis, it is preferred that the compounds of this invention are used to treat restenosis that occurs following an angioplasty procedure. When used for this purpose, the compounds of this invention can be administered prior to the procedure, during the procedure, subsequent to the procedure, or any combination of the above.

When administered for the treatment or inhibition of the above disease states, the compounds of this invention can be administered to a mammal orally, parenterally, intranasally, intrabronchially, transdermally, topically, intravaginally, or rectally.

It is contemplated that when the compounds of this invention are used as an immunosuppressive or anti-inflammatory agent, they can be administered in conjunction with one or more other immunoregulatory agents.

Such other immunoregulatory agents include, but are not limited to azathioprine, corticosteroids, such as prednisone and methylprednisolone, cyclophosphamide, rapamycin, cyclosporin A, FK-506, OKT-3, and ATG. By combining the compounds of this invention with such other drugs or agents for inducing immunosuppression or treating inflammatory conditions, the lesser amounts of each of the agents are required to achieve the desired effect. The basis for such combination therapy was established by Stepkowski whose results showed that the use of a combination of rapamycin and cyclosporin A at subtherapeutic doses significantly prolonged heart allograft survival time. [Transplantation Proc. 23: 507 (1991)].

The compounds of this invention can be formulated neat or with a pharmaceutical carrier to a mammal in need thereof. The pharmaceutical carrier may be solid or liquid. When formulated orally, it has been found that 0.01% Tween 80 in PHOSAL PG-50 (phospholipid concentrate with 1,2-propylene glycol, A. Nattermann & Cie, GmbH) provides an acceptable oral formulation.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methylcellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmotic regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compound can also be administered orally either in liquid or solid composition form.

The compounds of this invention may be administered rectally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semi-solid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

In addition, the compounds of this invention may be employed as a solution, cream, or lotion by formulation with pharmaceutically acceptable vehicles containing 0.1-5 percent, preferably 2%, of active compound which may be administered to a fungally affected area.

The dosage requirements vary with the particular compositions employed, the route of administration, the severity of the symptoms presented and the particular subject being treated. Based on the results obtained in the standard pharmacological test procedures, projected daily dosages of active compound would be 0.1 µg/kg-100 mg/kg, preferably between 0.001-25 mg/kg, and more preferably between 0.01-5 mg/kg. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached; precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated. Preferably, the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

The following examples illustrate the preparation and biological activities of representative compounds of this invention.

EXAMPLE 1

Rapamycin 42-ester with
(tetrahydropyran-2-yloxy)acetic acid

2,4,6-Trichlorobenzoyl chloride (0.55 mL, 3.51 mmol) was added via syringe to a solution of the glycolic acid THP-ether (0.562 g, 3.51 mmol) and triethylamine (0.49 mL, 3.51 mmol) in 10 mL THF at 0 ° C. under nitrogen. The mixture was stirred for 4 h at room

temperature, and a white precipitate formed. The white precipitate was removed by vacuum filtration and the filtrate was concentrated with a stream of nitrogen and warm water bath. The residue was dissolved in 10 mL benzene, then rapamycin (2.92 g, 3.19 mmol) and DMAP (0.429 g, 3.51 mmol) were added and the mixture was stirred overnight at room temperature. The mixture was diluted with EtOAc, washed with cold 1N HCl (aq), saturated NaHCO₃ (aq) and brine, dried over MgSO₄, filtered and concentrated to an oily yellow solid. Flash chromatography (2X with 65% EtOAc-hexane) afforded the title compound (1.114 g, 33%) as a white solid.

(-)FAB-MS *m/z* 1055.5 (M⁺), 590.3 (southern fragment), 463.2 (northern fragment). ¹H NMR (400 MHz, d-6 DMSO) δ 4.60 (m, 1H, C(42)H), 4.66 (m, 1H), 4.14 (s, 2H), 3.73 (m, 1H), 3.42 (m, 1H). ¹³C NMR (100.6 MHz, d-6 DMSO) δ 169.2, 97.4, 63.5, 61.2, 29.7, 24.8, 18.8.

EXAMPLE 2

Rapamycin 42-ester with hydroxyacetic acid

p-Toluenesulfonic acid (10 mg) was added to a solution of the product of Example 1 (306 mg, 0.29 mmol) in 10 mL CH₃OH at 0 ° C. The solution was stirred 2 h at room temperature, then quenched with saturated NaHCO₃ solution. The aqueous phase was extracted 3X with EtOAc and the combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated to a white solid. Purification by flash chromatography (2X with EtOAc) afforded the title compound (145 mg, 51%) as a white solid.

(-) FAB-MS *m/z* 971.3 (M⁺), 590 (southern fragment), 379.1 (northern fragment). ¹H NMR (400 MHz, d-6 DMSO) δ 4.60 (m, 1H, C(42)H), 3.98 (s, 2H). ¹³C NMR (100.6 MHz, d-6 DMSO) δ 172.1, 39.7.

Results obtained in standard pharmacological test procedures:

LAF IC₅₀: 1.80 nM

LAF ratio: 0.83

Percent change in adjuvant arthritis versus control: -88%

EXAMPLE 3

Rapamycin 42-ester with 2,2-dimethyl-3-(tetrahydropyran-2-yloxy)propionic acid

To a solution of the 2,2-dimethyl-3-hydroxypropionic acid THP-ether (0.319 g, 1.58 mmol) and triethylamine (0.22 mL, 1.58 mmol) in 5 mL dry THF at 0 ° C, under nitrogen was added 2,4,6-trichlorobenzoyl chloride (0.25 mL, 1.58 mmol) dropwise via syringe. The mixture was stirred 4.5 h at room temperature. The white precipitate was removed by vacuum filtration and the filtrate was concentrated with a stream of nitrogen and a warm water bath. The residue was dissolved in 5 mL benzene, then rapamycin (1.31 g, 1.43 mmol) and DMAP (0.193 g, 1.58 mmol) were added. The mixture was stirred overnight at room temperature, diluted with EtOAc, washed with 1N HCl (aq), saturated NaHCO₃ (aq), H₂O and brine, dried over MgSO₄, filtered and concentrated to a yellow oily solid. Flash chromatography (1X with 60% EtOAc-hexane, 1X with 55% EtOAc-hexane) afforded the title compound (0.356 g, 23%), as a white solid.

(-)FAB-MS *m/z* 1097.7 (M⁺), 590.4 (southern fragment), 505.3 (northern fragment). ¹H NMR (400 MHz, d-6 DMSO) δ 4.55 (m, 1H, C(42)H), 4.55 (m, 1H), 3.69

(m, 1H), 3.60 (m, 2H), 3.42 (m, 1H), 1.13 (s, 3H), 1.11 (s, 3H). ¹³C NMR (100.6 MHz, d-6 DMSO) δ 175.0, 98.0, 73.8, 60.7, 42.6, 30.0, 24.9, 22.0, 21.6, 18.7.

Results obtained in standard pharmacological test procedures:

LAF IC₅₀: 7.10 nM

LAF ratio: 0.34

EXAMPLE 4

Rapamycin 42-ester with 3-hydroxy-2,2-dimethylpropionic acid

p-Toluenesulfonic acid (10 mg) was added to a solution of the product of Example 3 (250 mg, 0.23 mmol) in 10 mL CH₃OH at 0 ° C. The solution was stirred 2 hours at room temperature, then quenched with saturated NaHCO₃ solution. The aqueous phase was extracted 3X with EtOAc and the combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated to a white solid. Purification by flash chromatography (2X with 75% EtOAc-hexane) afforded the title compound (103 mg, 45%) as a white solid.

(-) FAB-MS *m/z* 1013.3 (M⁺), 590.2 (southern fragment), 421.1 (northern fragment). ¹H NMR (400 MHz, d-6 DMSO) δ 4.48 (m, 1H, C(42)H), 3.39 (d, 2H), 1.06 (s, 6H). ¹³C NMR (100.6 MHz, d-6 DMSO) δ 175.5, 68.0, 44.1, 21.7.

Results obtained in standard pharmacological test procedures:

LAF IC₅₀: 0.80 nM

LAF ratio: 1.25

Skin graft survival time: 10.7 ± 0.5 days

EXAMPLES 5 AND 6

Rapamycin 42-ester with

2,2-dimethyl[1,3]dioxalane-4-carboxylic acid (Ex. 5)

Rapamycin 31,42-diester with

2,2-dimethyl[1,3]dioxalane-4-carboxylic acid (EX. 6)

2,4,6-Trichlorobenzoyl chloride (0.56 mL, 3.61 mmol) was added via syringe to a solution of the 2,3-dihydroxypropionic acid isopropylidene ketal (0.527 g, 3.61 mmol) and triethylamine (0.50 mL, 3.61 mmol) in 10 mL THF at 0 ° C, under nitrogen. The mixture was stirred 4 h at room temperature. The white precipitate was removed by vacuum filtration and the filtrate was concentrated with a stream of nitrogen and warm water bath. The residue was dissolved in 15 mL benzene and rapamycin (3.00 g, 3.28 mmol), then DMAP (0.441 g, 3.61 mmol) were added and the mixture was stirred overnight at room temperature. The mixture was diluted with EtOAc, washed with cold 1N HCl (aq), saturated NaHCO₃ (aq) and brine, dried over MgSO₄, filtered and concentrated to a yellow foam. Flash chromatography on silica gel (gradient elution: 50-60-7-5-100% EtOAc-hexane, 4X with 65% EtOAc-hexane) afforded the title compounds. The less polar 31,42-diester (0.415 g) eluted first and the more polar 42-monoester (0.601 g, 16%) eluted second, and were isolated as white solids.

EXAMPLE 5

(-)FAB-MS *m/z* 1041.4 (M⁺), 590.3 (southern fragment), 449.2 (northern fragment). ¹H NMR (400 MHz, d-6 DMSO) δ 4.6 (m, 1H, C(42)H), 4.6 (m, 1H), 4.20 (dd, 1H), 3.96 (m, 1H), 1.36 (s, 3H), 1.30 (s, 3H). ¹³C

NMR (100.6 MHz, d-6 DMSO) δ 170.5, 110.2, 73.4, 66.6, 25.7, 25.4.

EXAMPLE 6

(-)-FAB-MS m/z 1169.6 (M⁻). ¹H NMR (400 MHz, d-6 DMSO) δ 5.3 (m, 1H, C(31)H), 4.6 (m, 1H, C(42)H), 4.6 (m, 2H), 4.19 (t, 1H), 4.13 (t, 1H), 3.9 (m, 2H), 1.36 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H). ¹³C NMR (100.6 MHz, d-6 DMSO) δ 170.5, 169.2, 110.3, 110.2, 73.4, 66.6, 66.5, 25.8, 25.7, 25.4, 25.1.

Results obtained in standard pharmacological test procedures:

EXAMPLE 5

LAF IC₅₀: 1.20 nM
LAF ratio: 0.74

EXAMPLE 6

LAF IC₅₀: 1.30 nM
LAF ratio: 0.5

EXAMPLE 7

Rapamycin 42-ester with 2,3-dihydroxypropionic acid

A solution of the product of Example 5 (351 mg, 0.34 mmol) in 10 mL THF and 10 mL 1N HCl was stirred at room temperature for 6 h. The mixture was diluted with EtOAc, washed with saturated NaHCO₃ solution and brine, dried over MgSO₄, filtered and concentrated to an oil. Flash chromatography (1X with EtOAc, 1X with 10% MeOH-CH₂Cl₂, 1X with 5% MeOH-EtOAc) afforded the title compound (78 mg, 23%) as a white solid.

(-)-FAB-MS m/z 1001.2 (M⁻), 590.2 (southern fragment), 409.1 (northern fragment). ¹H NMR (400 MHz, d-6 DMSO) δ 5.45 (m, 1H, C(42)H), 3.60 (m, 1H), 3.43 (m, 2H).

Results obtained in standard pharmacological test procedures:

LAF IC₅₀: 1.4 nM
LAF ratio: 0.40

EXAMPLE 8

Rapamycin 42-ester with
2,2-dimethyl[1,3-dioxane-5-carboxylic acid

2,4,6-Trichlorobenzoyl chloride (0.98 mL, 6.27 mmol) was added via syringe to a solution of the 2-(hydroxymethyl)-3-hydroxypropionic acid isopropylidene ketal (1.000 g, 6.24 mmol) and triethylamine (0.90 mL, 6.46 mmol) in 20 mL THF at 0 ° C. under nitrogen. The mixture was stirred for 4 h at room temperature, and a white precipitate formed. The white precipitate was removed by vacuum filtration and the filtrate was concentrated with a stream of nitrogen and warm water bath. The residue was dissolved in 20 mL benzene, then rapamycin (5.70 g, 6.24 mmol) and DMAP (0.762 g, 6.24 mmol) were added and the mixture was stirred overnight at room temperature. The mixture was diluted with EtOAc, washed with H₂O and brine, dried over MgSO₄, filtered and concentrated to a yellow solid. Flash chromatography (75% EtOAc-hexane) afforded the title compound (4.17 g, 63%) as a white solid.

(-)-FAB-MS m/z 1055.8 (M⁻), 590.5 (southern fragment), 463.4 (northern fragment). ¹H NMR (400 MHz, d-6 DMSO) δ 4.55 (m, 1H, C(42)H), 3.95 (m, 4H), 1.30 (s, 6H). ¹³C NMR (100.6 MHz, d-6 DMSO) δ 170.1, 97.4, 59.5, 24.8, 22.5.

Results obtained in standard pharmacological test procedures:

LAF IC₅₀: 0.76 nM
LAF ratio: 0.45

EXAMPLE 9

Rapamycin 42-ester with
3-hydroxy-2-hydroxymethylpropionic acid

A solution of the product of Example 8 (3.30 g, 3.12 mmol) in 50 mL THF and 25 mL 1N HCl was stirred 2 h at room temperature. The solution was diluted with saturated NaHCO₃ solution and extracted with EtOAc (3X). The combined organic phases were washed with saturated NaCl (aq), dried over MgSO₄, filtered and concentrated to a yellow foam. Purification by flash chromatography (1X with EtOAc; 2X with 5% EtOH-EtOAc) afforded the title compound (1.68 g, 53 %) as a white solid.

(-)-FAB-MS m/z 1015.5 (M⁻), 590.3 (southern fragment), 423.3 (northern fragment). ¹H NMR (400 MHz, d-6 DMSO) δ 4.6 (br s, 2H), 4.55 (m, 1H, C(42)H), 3.55 (m, 4H), 2.57-2.53 (m, 1H). ¹³C NMR (100.6 MHz, d-6 DMSO) δ 172.2, 59.3, 51.5.

Results obtained in standard pharmacological test procedures:

LAF IC₅₀: 0.84 nM
LAF ratio: 0.57

EXAMPLE 10

Rapamycin 42-ester with
2,2,5-trimethyl[1,3-dioxane-5-carboxylic acid

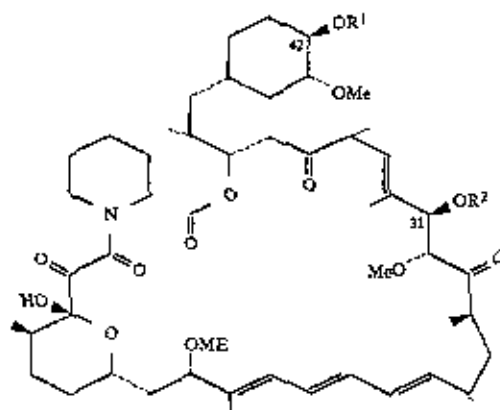
To a solution of the 2,2-bis(hydroxymethyl)propionic acid isopropylidene ketal (1.041 g, 5.98 mmol) (prepared according to the procedure of Bruce, J. Am. Chem. Soc. 89:3568 (1967)) and triethylamine (0.83 mL, 5.98 mmol) in 20 mL anhydrous THF at 0 ° C. under nitrogen was added 2,4,6-trichlorobenzoyl chloride (0.93 mL, 5.98 mmol) and the resultant white suspension was stirred 5 h at room temperature. The precipitate was removed by vacuum filtration, rinsing the flask and filter cake with an additional 10 mL dry THF. The filtrate was concentrated by rotary evaporation to a white solid. The residue was dissolved in 20 mL dry benzene, then rapamycin (5.47 g, 5.98 mmol) and DMAP (0.731 g, 5.98 mmol) were added. After stirring overnight at room temperature, the mixture was diluted with EtOAc, washed with H₂O and saturated NaCl (aq), dried over MgSO₄, filtered and evaporated to a yellow oil. Flash chromatography (5X with 60% EtOAc-hexane) afforded the title compound (2.2 g, 34%) as a white solid.

(-)-FAB-MS m/z 1069.5 (M⁻), 590.3 (southern fragment), 477.2 (northern fragment). ¹H NMR (400 MHz, d-6 DMSO) δ 4.57 (m, 1H, C(42)H), 4.02 (d, 2H), 3.60 (d, 2H), 1.34 (s, 3H), 1.24 (s, 3H), 1.06 (s, 3H). ¹³C NMR (100.6 MHz, d-6 DMSO) δ 173.2, 99.0, 65.0, 22.2, 18.1.

Results obtained in standard pharmacological test procedures:

LAF IC₅₀: 4.90 nM
LAF ratio: 0.41

Skin graft survival time: 11.0±1.3 days



wherein R^1 and R^2 are each, independently, hydrogen or $-\text{CO}(\text{CR}^3\text{R}^4)_b\text{CR}^5\text{R}^6\text{CR}^7\text{R}^8$;

R^3 and R^4 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, trifluoromethyl, or $-\text{F}$;

R^5 and R^6 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, $-(\text{CR}^3\text{R}^4)_c\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$, or R^5 and R^6 may be taken together to form X or a cycloalkyl ring of 3-8 carbon atoms that is optionally mono-, di-, or tri-substituted with $-(\text{CR}^3\text{R}^4)_c\text{OR}^{10}$;

R^7 is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, $-(\text{CR}^3\text{R}^4)_c\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$;

R^8 and R^9 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, $-(\text{CR}^3\text{R}^4)_c\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$, or R^8 and R^9 may be taken together to form X or a cycloalkyl ring of 3-8 carbon atoms that is optionally mono-, di-, or tri-substituted with $-(\text{CR}^3\text{R}^4)_c\text{OR}^{10}$;

R^{10} is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, tri-(alkyl of 1-6 carbon atoms)silyl, tri-(alkyl of 1-6 carbon atoms)silylethyl, triphenylmethyl, benzyl, alkoxyethyl of 2-7 carbon atoms, tri-(alkyl of 1-6 carbon atoms)silylethoxymethyl, chloroethyl, or tetrahydropyranyl;

R^{11} is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, or phenylalkyl of 7-10 carbon atoms;

X is 5-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxanyl, 5-(2,2-di-(cycloalkyl of 3-8 carbon atoms))[1,3]dioxanyl, 4-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxanyl, 4-(2,2-di-(cycloalkyl of 3-8 carbon atoms))[1,3]dioxanyl, 4-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxalanyl, or 4-(2,2-di-(cycloalkyl of 3-8 carbon atoms))[1,3]dioxalanyl;

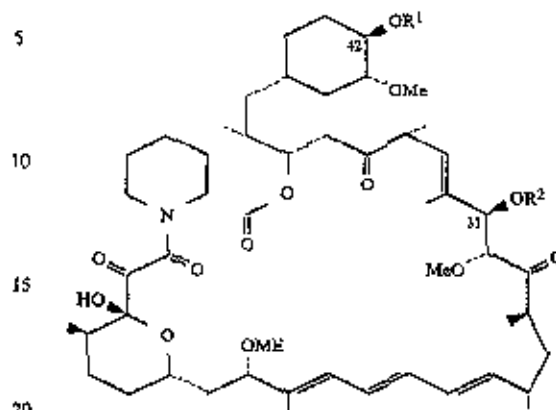
$b=0-6$;

$d=0-6$; and

$f=0-6$

with the proviso that R^1 and R^2 are both not hydrogen and further provided that either R^1 or R^2 contains at least one $-(\text{CR}^3\text{R}^4)_c\text{OR}^{10}$, X, or $-(\text{CR}^3\text{R}^4)_c\text{OR}^{10}$ substituted cycloalkyl of 3-8 carbon atoms group, or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition which comprises a compound of the structure



wherein R^1 and R^2 are each, independently, hydrogen or $-\text{CO}(\text{CR}^3\text{R}^4)_b\text{CR}^5\text{R}^6\text{CR}^7\text{R}^8$; R^3 and R^4 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, trifluoromethyl, or $-\text{F}$;

R^5 and R^6 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, $-(\text{CR}^3\text{R}^4)_c\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$, or R^5 and R^6 may be taken together to form X or a cycloalkyl ring of 3-8 carbon atoms that is optionally mono-, di-, or tri-substituted with $-(\text{CR}^3\text{R}^4)_c\text{OR}^{10}$;

R^7 is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, $-(\text{CR}^3\text{R}^4)_c\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$;

R^8 and R^9 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, $-(\text{CR}^3\text{R}^4)_c\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$, or R^8 and R^9 may be taken together to form X or a cycloalkyl ring of 3-8 carbon atoms that is optionally mono-, di-, or tri-substituted with $-(\text{CR}^3\text{R}^4)_c\text{OR}^{10}$;

R^{10} is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, tri-(alkyl of 1-6 carbon atoms)silyl, tri-(alkyl of 1-6 carbon atoms)silylethyl, triphenylmethyl, benzyl, alkoxyethyl of 2-7 carbon atoms, tri-(alkyl of 1-6 carbon atoms)silylethoxymethyl, chloroethyl, or tetrahydropyranyl;

R^{11} is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, or phenylalkyl of 7-10 carbon atoms;

X is 5-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxanyl, 5-(2,2-di-(cycloalkyl of 3-8 carbon atoms))[1,3]dioxanyl, 4-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxanyl, 4-(2,2-di-(cycloalkyl of 3-8 carbon atoms))[1,3]dioxalanyl, or 4-(2,2-di-(cycloalkyl of 3-8 carbon atoms))[1,3]dioxalanyl;

$b=0-6$;

$d=0-6$; and

$f=0-6$

with the proviso that R^1 and R^2 are both not hydrogen and further provided that either R^1 or R^2 contains at least one $-(\text{CR}^3\text{R}^4)_c\text{OR}^{10}$, X, or $-(\text{CR}^3\text{R}^4)_c\text{OR}^{10}$ substituted cycloalkyl of 3-8 carbon atoms group, or a pharmaceutically acceptable salt thereof, and a pharmaceutical carrier.

* * * * *

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogada
ALICIA LLOREDA RICAURTE
Apoderada

ASUNTO	Radicación	05033799
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	 5 9 4 9
	Folios	121

Patente de Invención		Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)		Cap. I	☐
		Cap. II	
No. Sol. Internacional	PCT/US2003/029228		
Fecha de Presentación Interna.	15/09/2003		

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción: Folios: 27 a 36, 67-68

Reivindicaciones: Folios 37 a 39
Folios 115 a 116

Prioridad: Fecha: 17/09/2002, país: US, número: 60/411.264

Respuesta del solicitante: Folios: 100 a 108

2. Objeto de la invención

- Título de la solicitud: Formulaciones orales sólidas de rapamicina 42-éster con ácido propiónico 3-hidroxi-2-(hidroximetil)-2-metil. Número de folio: 63

El problema planteado en esta solicitud es la necesidad de formulaciones útiles como antibióticos antifúngicos trieno macrocíclicos con efectos inmunodepresivos (antitumoral) en rechazo de transplantes, encefalomiелitis alérgica, esclerosis múltiple, artritis, lupus sistémico eritematoso, diabetes, psoriasis, etc.

Para solucionar este problema técnico la solicitud en estudio proporciona formulaciones orales sólidas de rapamicina éster con ácido 3-hidroxi-2-(hidroximetil) – 2- metil propiónico (CCI-779).

Clasificación Internacional de Patentes (IPC.): A61K 9/00

3. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 17/09/2002

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D ₁	US 2002/0091137	USE OF CCI-779 AS AN ANTINEOPLASTIC AGENT	11/07/2002
D ₂	US 5362718	RAPAMYCIN HYDROXYESTERS	8/11/1994

4. Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica:

Reivindicaciones 1-6, 9: Composición oral que comprende:

- una granulación
- CCI 779
- Polímero soluble en agua: PVP, hidroxipropilmetilcelulosa, polietilenglicol, ciclodextrina o mezclas.
- Surfactante: Polisorbato 80, lauril sulfato de sodio, dodecil sulfato de sodio, sal de ácido biliar, aceite vegetal etoxilado, copolímero de bloque polioxietileno- polioxipropileno, o un poloxámero.
- 0.01-1% p/p de un antioxidante: ácido cítrico, d,l- α -tocoferol, BHA, BHT, monotioglicerol, ácido ascórbico y propil galato
- Agente modificador de pH: citrato de sodio, ácido cítrico, ácido clorhídrico diluido y mezclas.

Reivindicación 7: Proceso para preparar una composición oral de CCI-779 que comprende:

- a) Disolver CCI-779 y 0.01 – 1% de un antioxidante en un alcohol
- b) Disolver PVP, un agente modificador de pH, y un surfactante en agua.
- c) Combinar las soluciones acuosa y alcohólica para proporcionar una solución hidroalcohólica.

- b) Disolver PVP, un agente modificador de pH, y un surfactante en agua
- c) Combinar las soluciones acuosa y alcohólica para proporcionar una solución hidroalcohólica.
- d) Adicionar la solución hidroalcohólica a una mezcla que contiene uno o más excipientes intragranulares
- e) Granular la mezcla
- f) Secar la granulación

Reivindicación 8: Proceso para preparar una composición oral de CCI-779 que comprende:

- a) Disolver CCI-779 y 0.01 – 1% de un antioxidante en un alcohol
- b) Disolver PVP, un agente modificador de pH, y un surfactante en agua.
- c) Adicionar las soluciones acuosa y alcohólica por pasos a una mezcla que contiene uno o más excipientes intragranulares
- d) Granular la mezcla
- e) Secar la granulación

Dicha composición se ve afectada por los siguientes documentos:

D₁ que enseña el uso de CCI-779 en el tratamiento de neoplasmas y formulaciones que los contienen (Ver folio: 86).

CARACTERÍSTICAS REIVINDICADAS 1-6	D ₁ folio 89 [0038]	D ₂
Una granulación	SI Folio 89 [0038]	-
CCI-779	SI Folio 86	SI Folio 93 cl 1 ln 5, 65, 94 cl 4, ln 38 y siguientes, folio 98 ej 9
Polímero soluble en agua: PVP, hidroxipropilmetilcelulosa, ciclodextrina o mezclas	SI Folio 89 [0038]	SI Cl 7
Surfactante: Polisorbato 80, lauri sulfato de sodio, dodecil sulfato de sodio, sal de ácido biliar, aceite vegetal etoxilado, copolímero de bloque polioxietileno- polioxipropileno, o un poloxámero	SI Folio 89 [0038]	SI Cl 7
0.01-1% p/p de un antioxidante: ácido cítrico, d,l- α -tocoferol, BHA, BHT, monoglicérol, ácido ascórbico y propil galato	NO	-
Agente modificador de pH: Citrato de sodio, ácido cítrico, ácido clorhídrico diluido y mezclas	SI Folio 89 [0038]	-

La única **diferencia con D₁** es que esta solicitud **utiliza antioxidantes** pero esta diferencia no parece conceder un efecto técnico inesperado.

No hay evidencia del **efecto técnico logrado** ya que este tipo de formulaciones logradas por granulación húmeda que aparentemente le otorga superioridad a la formulación se encontraba ya sugerida en D1.

De esta forma el **Problema Técnico Objetivo** se puede definir en como lograr

una formulación de CCI-779 alternativa a las previamente conocidas.

Si tenemos en cuenta los conocimientos de D₁ con D₂ donde se enseñan derivados de rapamicina, análogos hidroxiésteres y la rapamicina 42 éster con ácido propionico 3-hidroxi- 2- hidroximetil la solicitud se considerará obvia para un experto en la materia porque ya eran conocidas las posibles combinaciones para realizar formulaciones y los posibles procesos, de tal forma que resultaría obvio realizar formulaciones con este principio activo para lograr cambios en los resultados finales del producto.

Obtener una buena disolución in Vitro o una buena solubilidad acuosa, no puede llevar a suponer que la biodisponibilidad in vivo se va a presentar aumentada ya que es bien conocido en el medio que los parámetros que afectan la biodisponibilidad in vivo de un compuestos son multifactoriales y no dependen exclusivamente del resultado obtenido con las pruebas de solubilidad de un producto.

Los procesos reivindicados por **granulación húmeda** tampoco se consideran inventivos ya que se llevan a cabo de la forma como normalmente era conocido en la técnica realizar un proceso de fabricación de este tipo para un principio activo, es decir, disolver componentes en solventes, granular, tamizar, lubricar y comprimir (REMINGTON FARMACIA 19 edición, abril 1998, páginas 2481 y siguientes "Métodos de granulación").

Agregar antioxidantes ya era una práctica común en el diseño de formulaciones; así que un experto en la materia mediante la granulación y el principio activo sugeridos por D1 obtendría **las composiciones orales** reivindicadas.

En conclusión, no se considera que la presente solicitud merezca reconocimiento de nivel inventivo.

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D ₁	US 2002/0091137	1-8	NIVEL INVENTIVO
D ₂	US 5362718	1-8	NIVEL INVENTIVO

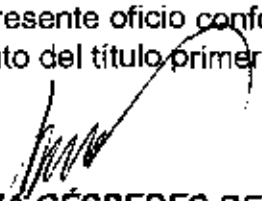
7. Respuesta a los argumentos del solicitante:

- Afirma el solicitante que es claro que en D1 no se tiene en cuenta el problema técnico abordado en la presente solicitud, no se mencionan y mucho menos se solucionan los problemas generados por la baja solubilidad en agua del compuesto CCI-779 durante la obtención de formulaciones farmacéuticas que comprendan dicho compuesto activo. No se enseña y tampoco se sugiere que una formulación granulada de CCI-779 pueda presentar una solubilidad en agua muy superior a la lograda cuando dicha formulación es obtenida mediante técnicas de compresión convencionales.

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- Si bien el problema técnico a solucionar por D1 no consistía en los problemas generados por la baja solubilidad en agua del compuesto CCI-779, sí se sugería allí realizar formulaciones en procesos de granulación húmeda con el compuesto en mención. Por lo tanto si se siguiera lo sugerido por D1 un experto en la materia notaría que se aumenta la solubilidad del compuesto así el documento no lo mencione.
 - Se reconoce la formulación farmacéutica reivindicada como novedosa más no se reconoce su nivel inventivo tal como se muestra en el primero y segundo examen de fondo.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
22 MAYO 2009

CONCEPTO TÉCNICO No. 327	EXAMINADOR TÉCNICO Código No. 202087
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