



Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No.

06-55468

54. TITULO "PROCESO PARA LA PREPARACION DE
INHIBIDORES DE TUBULINA"

51. CLASIFICACION INTERNACIONAL C07D 487/04

71. SOLICITANTE WYETH

DOMICILIO NUOVA JERSEY, ESTADO UNIDO

74. APODERADO ALVARO CORREA ORTIZ
T.P. 20.281

22. BOGOTA, D.C., JUNIO 8, 2006

Publicacion
10-07-2006

PETITORIO

000001

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-055468-00000-0000
Fec. 2006-06-08 16:05:56 Dep. 2020 NUECREACIONES
Tra. 11 PATENTE/II
Evo: 378 FASENACIONAL
Act 411 PRESENTACION

Folios: 102

dicación

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

①

SOLICITUD DE :

☒

Patente de Invención

☐

Patente de Modelo de Utilidad

☒

Capítulo I.

☐

Capítulo II.

②

SOLICITANTE
(71)

Nombre. WYETH

Dirección Five Giralda Farms, Madison, NJ 07940 Estados Unidos de América

Nacionalidad o Domicilio. Nueva Jersey, Estados Unidos de América
Lugar de Constitución.

Teléfono

Fax

E-Mail

IDENTIFICACION

C C

☐

NIT

☐

C E.

☐

Otro

☐

Cual

Número

③

REPRESENTANTE
O APODERADO

Nombre. ALVARO CORREA ORDOÑEZ

Dirección Avenida 82 No 10-62 Piso 6

Teléfono 634 1500

Fax 376 2211

E-Mail office bogota@bakernet.com

IDENTIFICACION

C C

☒

NIT

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C E.

☐

Otro

☐

Cual

Número 79 143 366 U/quen TP 20 281

④

INVENTOR (ES)
(72)

Nombre WU, Yanzhong, SCHMID, Jean, AFRAGOLA, Jay Thomas, BLUM, David Michael, AYRAL-KALOUSTIAN, Semiramis

Dirección. 1580 Pelham Parkway South, Apartment 4K, Bronx, NY 10461 (US), 17 Jeffrey Drive, Chester, NY 10918 (US), 141 Heitman Drive, Apartment F, Spring Valley, NY 10977 (US), 3 Saddle Horn Drive, Upper Saddle River, NY 07458 (US), 484 Carrollwood Drive, Tarrytown, NY 10591(US)

Nacionalidad o Domicilio Estadounidense, Canadiense, Estadounidense, Estadounidense y Estadounidense, respectiva/

⑤

PCT (85)

Solicitud Internacional No PCT/US2004/040854

Fecha 07-DIC-04

Publicación Internacional No WO 2005/056560 A1

Fecha 23-JUN-05

⑥

Título (54)

PROCESO PARA LA PREPARACIÓN DE INHIBIDORES DE TUBULINA

⑦

Clasificación Internacional (51)

C07D 487/04

⑧

Prioridad

SI ☒NO ☐

(33) País de Origen

US

(32) Fecha

08-DIC-03

(31) Número de Solicitud

60/527 931

⑨

Comprobante de pago No. 06-41598

Fecha 02-JUN-06

10

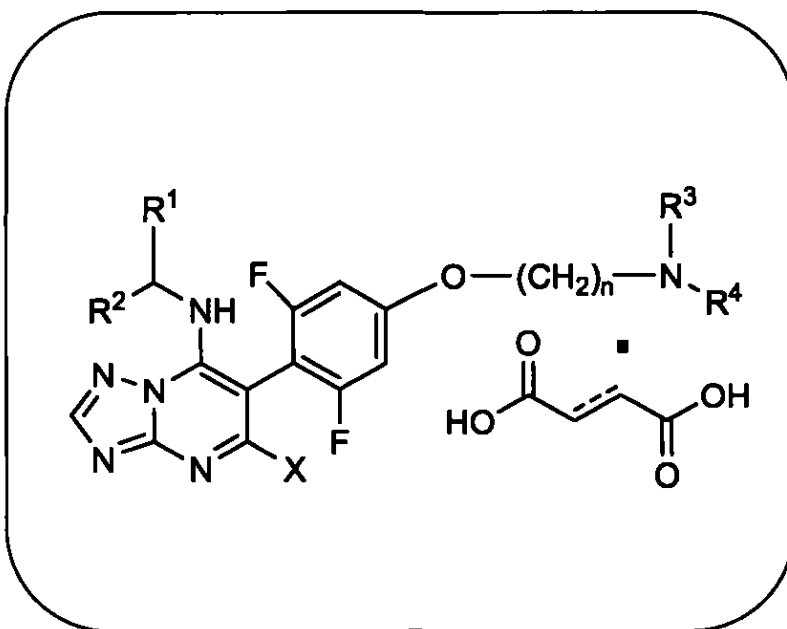
ANEXOS

999002

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- ☐ Poderes, si fuere el caso
- ☒ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional
- ☒ Otros Extractos publicación, propietario y temático, reporte de búsqueda

11

FIGURA CARACTERISTICA



12

Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79 143 366 de Usaquén T.P. 20.281

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

000803-010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 08-055468-00000-0000
Fec: 2006-06-08 16:06:56 Dep. 2020 NUECREACIONES
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Act 411 PRESENTACION Folios. 102

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 41,598
FECHA : JUNIO 2 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
RAISBECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	36559816	02/06/2006	30,057,000.00

***** CONCEPTO *****

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

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

TRADUCCIÓN OFICIAL No. 208/06 de un documento escrito en inglés, el cual para su identificación se sella con el sello del Traductor. Esta es una Traducción Oficial efectuada el día 5 de junio de 2006 por la Sra. María Teresa Lara, c.c. 41.568.055 de Bogotá, Traductora Oficial según Resolución No. 01016 del 2 de octubre de 1998, expedida por el Ministerio de Justicia.

= = = = =

Declaración Juramentada (Affidavit) de WYETH respecto de solicitud de patente para "Proceso para la Preparación de Inhibidores de la Tubulina".
Certificación notarial suscrita por Barbara A. Kiely, Notario Público del estado de Nueva Jersey, y legalizaciones subsiguientes.

AM101480L

DECLARACIÓN JURAMENTADA

Yo, Michelle L. McGowan, Asociada para Legalizaciones, Wyeth, certifico por la presente que la copia adjunta ha sido comparada con la Cesión original (para el expediente No. AM101480L de Wyeth correspondiente a la U.S.S.N. 60/527,931, y cualquier equivalente legal de la misma en un país extranjero, para el invento titulado: "PROCESO PARA LA PREPARACIÓN DE INHIBIDORES DE LA TUBULINA") fechada el 8 de diciembre de 2003 de Yanzhong Wu, Jean Schmid, Jay Thomas Afragola, David Blue y Semiramis Ayrat-Kaloustian a Wyeth y que la citada copia es fiel copia del original.

Dado a los 8 días del mes de febrero de 2006, en Madison, Nueva Jersey, Estados Unidos de América.

Wyeth

(Fdo.) Michelle L. McGowan

Michelle L. McGowan
Asociada para Legalizaciones


 MARIA TERESA LARA R.
 TRADUCTORA OFICIAL
 RESOLUCION No. 01016
 DE JUSTICIA

PARA USO EN COLOMBIA

RECONOCIMIENTO

Estado de Nueva Jersey)
)
 Condado de Morris)

A los 8 días del mes de febrero de 2006, ante mi personalmente compareció Michelle L. McGowan, Asociada para Legalizaciones de Wyeth, a quien conozco y de quien me consta que es la persona descrita en el instrumento anterior y quien lo suscribió, y reconoció ante mi haber suscrito el mismo.

(Fdo.) Barbara A. Kiely
Notario Público

**(Sello notarial
en relieve)**

[Sello] Barbara A. Kiely ID. 33893
Notario Público de Nueva Jersey
MI comisión expira el 20 de junio de 2009

'RIA TERESA LARA R.
TRADUCTORA C.P.C.R.
RESOLUCION 74-2170
DE MINJUSTICIA

Expediente No: AM101480 L1
Patente

Para: ☒ Derechos en los E.U. y/o ☒ Extranjeros
Para: ☒ Solicitud en los E.U. o ☐ Patente de los E.U.

Cesión de Inventario

En virtud del pago por la CESIONARIA al CEDENTE de contraprestación válida, el recibo de la cual se reconoce por el presente, el CEDENTE:

(1) **Nombre Completo del Inventor:** Yanzhong WU
Residencia: 1580 Pelham Parkway S., Apt. 4K, Bronx, NY 10461
Ciudadanía: Estados Unidos de América

(2) Nombre Completo del Inventor: Jean SCHMID
Residencia: 17 Jeffrey Drive, Chester, NY 10918
Ciudadanía: Canadá

(3) Nombre Completo del Inventor: Jay Thomas AFRAGOLA
Residencia: 141 Heltman Drive, Apt. F, Spring Valley, NY 10977
Ciudadanía: Estados Unidos de América

(4) Nombre Completo del Inventor: David BLUM
Residencia: 3 Saddle Horn Drive, Upper Saddle River, NJ 07458
Ciudadanía: Estados Unidos de América

(5) Nombre Completo del Inventor: Semiramis AYRAL-KALOUSTIAN
Residencia: 484 Carrollwood Drive, Tarrytown, NY 10591
Ciudadanía: Estados Unidos de América

TERESA LARA R.
TRADUCTORA CERTIFICADA
REGOLUCION No. 27816
DE MINISTERIO

por la presente vende, cede y traspasa a la CESIONARIA:

Wyeth
Five Giralda Farms
Madison, Nueva Jersey 07940

y los sucesores, cesionarios y representantes legales de la CESIONARIA, todo derecho, título e interés para los Estados Unidos y sus posesiones territoriales y en todos los países extranjeros, incluyendo todo los derechos a reclamar prioridad, en y sobre el invento titulado:

PROCESO PARA LA PREPARACIÓN DE INHIBIDORES DE LA TUBULINA

e inventado por la CEDENTE y los siguientes Inventores adicionales, en caso de haberlos:

y la cual se encuentra en

[marcar y completar (a), (b), (c), (d) o (e)]

(a) [] solicitud de patente de los E.U. de igual fecha que la presente

(b) [] solicitud de patente de los E.U. suscrita el:

- (c) ☒ solicitud provisional de los E.U., no presentada aún, que nombra al(los) inventor(es) anterior(es) para el invento de la referencia

☒ etiqueta de correo expreso no.: EU673382125US

- (d) [] Solicitud de Patente de los E.U. No. _____ presentada el: _____

- (e) ☐ Patente de los E.U. No. _____ expedida el: _____

[marcar también si se están cediendo solicitud(es) extranjera(s)]

- (f) ☒ y cualquier equivalente legal de las mismas en un país extranjero,

incluyendo el derecho a reclamar prioridad, incluidas todas y cada una de las mejoras allí divulgadas, y en y sobre todas las Patentes que hayan de obtenerse para dicho invento en virtud de la solicitud anterior o cualquier solicitud provisional, no provisional, de continuación, divisional, de renovación o sustituta de la misma posteriormente presentada, y respecto de Patentes cualquier reemisión o reexamen de las mismas.

El CEDENTE pacta por el presente que no se ha hecho ni se hará ni se realizará ninguna cesión, venta, acuerdo o gravamen que pudiese entrar en conflicto con esta cesión.

El CEDENTE autoriza a la CESIONARIA a presentar solicitudes y recibir Patentes para dicho invento en cualquiera de dichos países en su propio nombre, o en nombre de la CEDENTE, a su elección.

El CEDENTE pacta y acuerda suscribir u obtener cualquier garantía adicional necesaria del título sobre dicho invento y cualquier Patente que pueda emitirse para la misma, en cualquier momento, y a solicitud y por cuenta de la CESIONARIA entregar cualquier testimonio en cualquier interferencia, litigio o proceso relacionado con la misma y otorgar todos los

PIA TERESA LARA R.
TRADUCTORA OFICINA
RESOLUCION No. 21810
JE MINUTISTELA

documentos que puedan ser necesarios o convenientes para perfeccionar el título sobre dicho invento o cualquier Patente que pueda otorgarse para la misma en la CESIONARIA, sus sucesores, cesionarios u otros representantes legales y que, en cualquier momento, a solicitud y por cuenta de la CESIONARIA suscriba cualquier continuación, continuación en parte, solicitud divisional, renovación o sustituta de la misma, y en cuanto a Patentes y reemisión o reexamen de las mismas, o cualquier otra solicitud adicional de Patente para dicho invento o cualquier parte del mismo, todas las cuales solicitudes y cualesquiera Patentes que se expidan sobre las mismas son por la presente cedidas a la CESIONARIA, y hará todo los juramentos o declaraciones lícitos, y realizará todo los actos lícitos requeridos para adquirir las mismas, sin otra compensación, pero por cuenta de la CESIONARIA, sus sucesores, cesionarios u otros representantes legales.

El CEDENTE autoriza y solicita al Comisionado de Patentes expedir todas y cada una de las Patentes de los Estados Unidos para dicho invento, resultantes de cualquiera de las anteriores solicitudes para su CESIONARIA.

(Fdo.) Yanzhong WU
Yanzhong WU

Dic. 8, 2003
Fecha

RECONOCIMIENTO

Estado de Nueva York }
 ss:
Condado de Rockland }

A los 8 días del mes de diciembre de 2003, compareció personalmente ante mí Yanzhong WU, a quien conozco como la misma persona descrita y que otorgó el instrumento anterior, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

YANZONG WU
TRADUCTORA OFICIAL
RESOLUCION No. 91876
DE MINISTROS

(Fdo.) Daniel B. Moran
Notario Público

[Sello] DANIEL B. MORAN
Notario Público, Estado de Nueva York
No. 01MO4944023
Habilitado en el Condado de Rockland
La comisión expira el 14 de noviembre de 2006

(Fdo.) Jean SCHMID
Jean SCHMID

Dic. 8, 2003
Fecha

RECONOCIMIENTO

Estado de Nueva York }
ss:
Condado de Rockland }

A los 8 días del mes de diciembre de 2003, compareció personalmente ante mí
Jean SCHMID, a quien conozco como la misma persona descrita y que otorgó
el instrumento anterior, y reconoció haber otorgado el mismo, por su propia
voluntad y para los propósitos allí señalados.

(Fdo.) Daniel B. Moran
Notario Público

[Sello] DANIEL B. MORAN
Notario Público, Estado de Nueva York
No. 01MO4944023
Habilitado en el Condado de Rockland
La comisión expira el 14 de noviembre de 2006

(Fdo.) Jay Thomas Afragola
Jay Thomas AFRAGOLA

Diciembre 8, 2003
Fecha

RECONOCIMIENTO

TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION N.º 9176
DE MINISTERIA

Estado de Nueva York }
 ss:
Condado de Rockland }

A los 8 días del mes de diciembre de 2003, compareció personalmente ante mí Jay Thomas AFRAGOLA, a quien conozco como la misma persona descrita y que otorgó el instrumento anterior, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Daniel B. Moran
Notario Público

[Sello] DANIEL B. MORAN
Notario Público, Estado de Nueva York
No. 01MO4944023
Habilitado en el Condado de Rockland
La comisión expira el 14 de noviembre de 2006

MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 1819
DE MINISTERIO DE JUSTICIA

(Fdo.) David Blum
David BLUM

Diciembre 8, 2003
Fecha

RECONOCIMIENTO

Estado de Nueva York }
 ss:
Condado de Rockland }

A los 8 días del mes de diciembre de 2003, compareció personalmente ante mí David BLUM, a quien conozco como la misma persona descrita y que otorgó el instrumento anterior, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Daniel B. Moran
Notario Público

[Sello] DANIEL B. MORAN
Notario Público, Estado de Nueva York
No. 01MO4944023
Habilitado en el Condado de Rockland
La comisión expira el 14 de noviembre de 2006

(Fdo.) Semiramis Ayrál-Kaloustian
Semiramis AYRAL-KALOUSTIAN

Dic. 8, 2003
Fecha

RECONOCIMIENTO

Estado de Nueva York }
 ss:
Condado de Rockland }

A los 8 días del mes de diciembre de 2003, compareció personalmente ante mí Semiramis AYRAL-KALOUSTIAN, a quien conozco como la misma persona descrita y que otorgó el instrumento anterior, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Daniel B. Moran
Notario Público

[Sello] DANIEL B. MORAN
Notario Público, Estado de Nueva York
No. 01MO4944023
Habilitado en el Condado de Rockland
La comisión expira el 14 de noviembre de 2006

TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION N.º 1878
DE MINISTROS

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. País: Estados Unidos de América
2. Este documento público ha sido firmado por: Barbara A. Kiely
3. actuando en calidad de: Notario Público de Nueva Jersey
4. lleva el sello/timbre de: Barbara A. Kiely, Notario

CERTIFICADO

5. en Trenton, Nueva Jersey
6. el día 10 de febrero de 2006
7. por Bradley I. Abelow, TESORERO DE NUEVA JERSEY

8. No. A251415

9. Sello/Timbre:

(Sello del Estado
de Nueva Jersey)

10. Firma

(Fdo.) Bradley Abelow

= = = = =

La anterior es traducción fiel y completa del documento en referencia, de la cual se deja copia en este archivo para su confrontación.



María Teresa Lara R.
c.c. 41.568.055 de Bogotá
Traductora Oficial según
Resolución No. 01016 del
2 de octubre de 1998, del
Ministerio de Justicia



MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 01016
DE MINISTERIO DE JUSTICIA

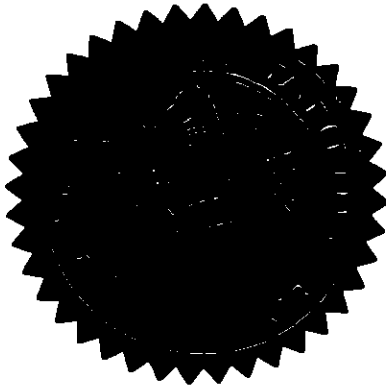
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

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

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 10TH DAY OF FEBRUARY 2006
7. BY: Bradley I. Abelow, NEW JERSEY TREASURER
8. NO. A251415
9. SEAL/STAMP:
10. SIGNATURE

Bradley Abelow*W780013*

Maria Teresa Lara R.

MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION N° 8187
DE MINISTERIA

208/06

AM101480L

AFFIDAVIT

I, Michelle L. McGowan, Legalization Associate, Wyeth, do hereby certify that the attached copy has been compared with the original Assignment (for Wyeth's Docket No. AM101480L corresponding to U.S.S.N. 60/527,931, and any legal equivalent thereof in a foreign country, for the invention entitled: "PROCESS FOR THE PREPARATION OF TUBULIN INHIBITORS") dated December 8, 2003 from Yanzhong Wu, Jean Schmid, Jay Thomas Afragola, David Blum and Semiramis Ayral-Kaloustian to Wyeth and that the said copy is a true copy of the original.

Dated this 8th day of February, 2006, at Madison, New Jersey, United States of America.

Wyeth

Michelle L. McGowan
Michelle L. McGowan
Legalization Associate

TO BE USED IN COLOMBIA

ACKNOWLEDGMENT

State of New Jersey)
)
County of Morris)

On this 8th day of February, 2006, before me personally appeared Michelle L. McGowan, Legalization Associate of Wyeth, to me known and known to me to be the individual described in and who executed the foregoing instrument, and he acknowledged to me that he executed the same.

Barbara A. Kiely
Notary Public

Barbara A. Kiely ID. 33893
Notary Public of New Jersey
My Commission Expires June 20, 2009

For: ☒ U.S. and/or ☒ Foreign Rights
For: ☒ U.S. Application or ☐ U.S. Patent

Assignment of Invention

In consideration of the payment by ASSIGNEE to ASSIGNOR of good and valuable consideration, the receipt of which is hereby acknowledged,
ASSIGNOR:

(1) Full Name of Inventor: Yanzhong WU
Residence: 1580 Pelham Parkway S., Apt 4K, Bronx, NY 10461
Citizenship: United States of America

(2) Full Name of Inventor: Jean SCHMID
Residence: 17 Jeffrey Drive, Chester, NY 10918
Citizenship: ~~Canadian~~ Canada U.S. *J.B.M.*

(3) Full Name of Inventor: Jay Thomas AFRAGOLA
Residence: 141 Hertman Drive, Apt. F, Spring Valley, NY 10977
Citizenship: United States of America

(4) Full Name of Inventor: David BLUM
Residence: 3 Saddle Horn Drive, Upper Saddle River, NJ 07458
Citizenship: United States of America

(5) Full Name of Inventor: Semiramis AYRAL-KALOUSTIAN
Residence: 484 Carrollwood Drive, Tarrytown, NY 10591
Citizenship: United States of America

(6) Full Name of Inventor:
Residence:
Citizenship:

hereby sells, assigns and transfers to ASSIGNEE

Wyeth
Five Giralda Farms
Madison, New Jersey 07940

and the successors, assigns and legal representatives of the ASSIGNEE the entire right, title and interest for the United States and its territorial possessions and in all foreign countries, including all rights to claim priority, in and to the invention entitled:
PROCESS FOR THE PREPARATION OF TUBULIN INHIBITORS

and invented by ASSIGNOR and the following additional inventors, if any:

and which is found in

[check and complete (a), (b), (c), (d) or (e)]

- (a) ☐ U.S. patent application executed on even date herewith.
(b) ☐ U.S. patent application executed on.
(c) ☒ U.S. provisional application, not yet filed, naming the above inventor(s) for the above-entitled invention
☒ Express mail label no.: EU673382125US
(d) ☐ U.S. Patent Application No. filed on:
(e) ☐ U.S. Patent No. issued on

[also check (f) if foreign application(s) is(are) also being assigned]

- (f) ☒ and any legal equivalent thereof in a foreign country,

including the right to claim priority, including any and all improvements disclosed therein, and in and to all Letters Patent to be obtained for said invention by the above application or any subsequently filed provisional, nonprovisional, continuation, divisional, renewal, or substitute thereof, and as to Letters Patent any reissue or re-examination thereof.

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment.

ASSIGNOR authorizes ASSIGNEE to make applications for and to receive Letters patent for said invention in any of said countries in its own name, or in ASSIGNOR's name, at its election.

ASSIGNOR covenants and agrees to execute or procure any further necessary assurance of the title to said invention and any Letters Patent which may issue therefore and to, at any time, upon the request and at the expense of ASSIGNEE deliver any testimony in any interference, litigation or proceeding related thereto and execute all papers that may be necessary or desirable to perfect the title to said invention or any Letters Patent which may be granted therefore in ASSIGNEE, its successors, assigns or other legal representatives, and that to, at any time, upon the request and at the expense of ASSIGNEE execute any continuation, continuation-in-part, divisional, renewal or substitute thereof, and as to Letters Patent and reissue or re-examination thereof, or any other additional applications of Letters Patent for said invention or any part thereof, all of which applications and any Letters Patent issuing thereon are hereby assigned to ASSIGNEE, and will make all rightful oaths or declarations, and do all lawful acts requisite for procuring the same therein, without further compensation, but at the expense of ASSIGNEE, its successors, assigns or other legal representatives.

ASSIGNOR authorizes and requests the Commissioner of Patents to issue any and all Letters Patent of the United States for said invention, resulting from any of the aforesaid applications to its ASSIGNEE

Yanzhong WU
Yanzhong WU

Dec 8, 2003
Date

ACKNOWLEDGMENT

State of New York }
County of Rockland } ss:

On the 8th day of December 2003, Yanzhong WU personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

DANIEL B. MORAN
Notary Public, State of New York
No. 01MO4944023
~~Qualified in Rockland County~~
Commission Expires Nov. 14, 2006

Daniel B. Moran
Notary Public

Jean Schmid
Jean SCHMID

Dec 8, 2003
Date

ACKNOWLEDGMENT

State of New York }
County of Rockland } ss:

On the 8th day of December 2003, Jean SCHMID personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

DANIEL B. MORAN
Notary Public, State of New York
No. 01MO4944023
Qualified in Rockland County
Commission Expires Nov. 14, 2006

Daniel B. Moran
Notary Public

Jay Thomas AFRAGOLA
Jay Thomas AFRAGOLA

December 8, 2003
Date

ACKNOWLEDGMENT

State of New York }
County of Rockland } ss:

On the 8th day of December 2003, Jay Thomas AFRAGOLA personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

DANIEL B. MORAN
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Qualified in Rockland County
Commission Expires Nov. 14, 2006

[Signature]
Notary Public

[Signature]
David BLUM

December 8, 2003
Date

ACKNOWLEDGMENT

State of New York }
County of Rockland } ss:

On the 8th day of December 2003, David BLUM personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth

DANIEL B. MORAN
Notary Public, State of New York
No. 01MO4944023
Qualified in Rockland County
Commission Expires Nov. 14, 2006

[Signature]
Notary Public

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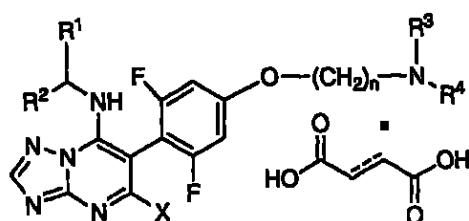
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[Continued on next page]

(54) Title: PROCESS FOR THE PREPARATION OF TUBULIN INHIBITORS



(I)

(57) Abstract: The present invention provides
a process for the preparation of 6-[(substituted)
phenyl]-triazolopyrimidine dicarboxylic acid
salt and as a hydrated salt having the structural
formula (I) wherein R¹ is CF₃ or C₂F₅, R² is
H or C₁-C₃ alkyl, n is an integer of 2, 3, or 4, X
is Cl or Br; R³ and R⁴ are each independently
H or C₁-C₃ alkyl, or R³ and R⁴ when optionally
taken together with the nitrogen atom to which
each is attached form a 4 to 6 membered

saturated heterocyclic ring having 1-2 nitrogen atoms and 0-1 oxygen atoms or 0-1 sulfur atoms, and optionally substituted with R⁵,
R⁵ is C₁-C₃ alkyl, wherein the dotted line is an optional bond

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PROCESS FOR THE PREPARATION OF TUBULIN INHIBITORS

FIELD OF THE INVENTION

5 The present invention relates to a process for the preparation of triazolopyrimidine dicarboxylic acid salts which are tubulin inhibitors useful in the treatment of cancer.

BACKGROUND OF THE INVENTION

10

 There is still a need in the art for cytotoxic agents for use in cancer therapy. In particular, there is a need for cytotoxic agents which inhibit or treat the growth of tumors which have an effect similar to paclitaxel and interfere with the process of microtubule formation. Additionally, there is a need in the art for agents which
15 accelerate tubulin polymerization and stabilize the assembled microtubules.

15

 Antimicrotubule drugs are a major category of anticancer agents (Rowinsky, E.K., and Tolcher, A.W. Antimicrotubule agents. In: V.T. Devita, Jr., S. Hellman, and S.A. Rosenberg (eds.), Cancer Principles and Practice, Ed. 6, pp. 431-452. Philadelphia: Lippincott Williams and Wilkins, 2001). Antimicrotubule drugs work by
20 interfering with the function of cellular microtubules, particularly the mitotic spindle. The disruption of normal spindle function leads to apoptotic cell death.

20

 Many tumors are inherently resistant (e.g., colon tumors) or become resistant after multiple cycles of treatment, at least in part due to the expression of drug transporters located in cancer cell membranes that pump the drugs out of cells and
25 thereby decrease their efficacy (Gottesman, M.M. Mechanisms of cancer drug resistance. Annu. Rev. Med., 53: 615-627, 2002). The best known of these transporters is P-glycoprotein. Accordingly, there is a need for new agents with taxane-like effects on microtubule polymerization that are not substrates of P-glycoprotein or other such pumps and that therefore will overcome this cause of
30 taxane resistance in patients.

30

 It is an advantage to provide new compounds which provide a method of treating or inhibiting cell proliferation, neoplastic growth and malignant tumor growth in mammals by administering compounds which have paclitaxel like anticancer

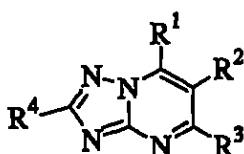
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activity. It is an additional advantage to provide new compounds which provide a method for treating or inhibiting growth of cancerous tumors that express multiple drug resistance (MDR) or are resistant because of MDR. It is an additional advantage to provide new compounds which provide a method of treating or inhibiting the growth of cancerous tumors in a mammal with inherent or acquired resistance to chemotherapeutic agents and in particular antimitotic agents.

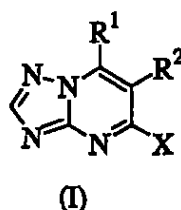
Accordingly, while there is ongoing research for new clinical candidates there is also a search for new and improved methods of preparation of those selected clinical candidates.

Described in WO 02/02563 A2 is the use of triazolopyrimidines having the structural formula



In cancer therapy, and in particular as microtubule agents. Previously described in US Patent numbers: 5,593,996; 5,758,509; 5,948,783; 5,981,534; 5,612,345; 5,994,360; 6,020,338; 5,985,883; 5,854,252; 5,808,066; 5,817,663; 5,955,252; 5,965,561; 5,988,153; 5,750,766; 6,117,876; 6,297,251 and International Publication Numbers: WO98/46607; WO98/46608; WO99/48893; WO99/41255; EPO 834513A2; EPO 782997A2; EPO550113B1; FR2784381A1; EPO 989130A1; WO98/41496; WO94/20501; EPO 945453A1; EPO 562615A1; EP 077065 and EPO 562615B1 are the methods of preparation and the use of the above triazolopyrimidines in agriculture as fungicides.

Described in copending case Docket No. AM 101270, application number 60/505,544, filed September 24, 2003 is a series of 6-[(substituted)phenyl]-triazolopyrimidine compounds having the structural formula



which are microtubule inhibitors and useful in the treatment of cancer.

Often, a process which works in the laboratory is not practical for large-scale preparations. In particular, the reported synthesis of 5,7-dichloro-6-(substituted-phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine prepared by cyclization of 2-(substituted-phenyl)-malonic acid diethyl ester with 1-amino-2,3,5-triazole is described in US 6,117,876 and further described in EP 0 770 615 A1 and EP 0 770 615 B1 where 6-(substituted-phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-5,7-diol is formed and chlorinated by reaction with phosphorus oxychloride to give 5,7-dichloro-6-(substituted-phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine. While the described series of steps may be completed on a small scale in a single vessel, the addition of chlorinating reagent, phosphorous oxychloride at 130°C following removal of ethanol by distillation, is difficult to perform in large-scale preparations. Further the above described process is limited to small-scale synthesis because the resulting product as an oil is difficult to purify.

US 5,986,135 and US 6,117,876 describe a method for the preparation of [5-chloro-6-(substituted-phenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-((1*S*)-2,2,2-trifluoro-1-methyl-ethyl)-amine, through amination of 5,7-dichloro-6-(substituted-phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine with (*S*)-2,2,2-trifluoro-1-methyl-ethylamine. The method however is not entirely satisfactory because an oily intermediate, which lacks a practical method of purification, is formed when preparing the 5,7-dichloro-6-(substituted-phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine and further the subsequent reaction with (*S*)-2,2,2-trifluoro-1-methyl-ethylamine is performed.

Clearly there is need to provide a new process for the preparation of 6-[(substituted)phenyl]-triazolopyrimidine compounds which overcomes the drawbacks of the prior art processes. In particular, there is a need for a process to prepare purified crystalline 6-[(substituted)phenyl]-triazolopyrimidine compounds.

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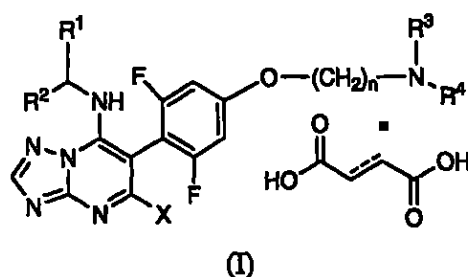
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Further there is a need to provide a new process which in comparison with those described in the above mentioned art represents a significant advance over the art.

In light of the usefulness of the triazolopyrimidine compounds in cancer therapy, there is a need to develop simpler and milder methods for their preparation.

SUMMARY OF THE INVENTION

The present invention provides a process for the preparation of a 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt and as a hydrated salt having the structural formula (I)



wherein:

R^1 is CF_3 or C_2F_5 ;

R^2 is H or C_1-C_3 alkyl;

n is an integer of 2, 3, or 4;

X is Cl or Br;

R^3 and R^4 are each independently H or C_1-C_3 alkyl; or

R^3 and R^4 when optionally taken together with the nitrogen atom to which each is attached form a 4 to 6 membered saturated heterocyclic ring having 1-2 nitrogen atoms and 0-1 oxygen atoms or 0-1 sulfur atoms, and optionally substituted with R^5 ;

R^5 is C_1-C_3 alkyl;

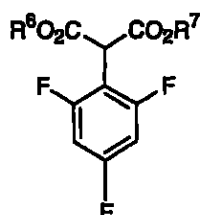
wherein the dotted line is an optional bond,

which process comprises:

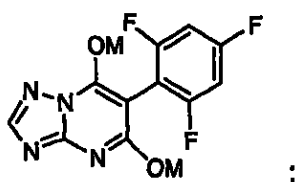
a. reacting a malonic acid ester of the formula

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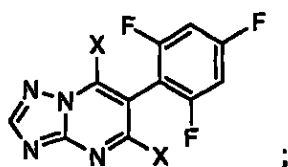


- where R^6 and R^7 are independently C_1 - C_3 alkyl with 3-amino-1,2,4-triazole, in the presence of trialkylamine base and heating at about 130-170°C, for about 1 to 6 h,
 5 cooling to about 130° C, diluting with toluene, cooling from about 20°C to about 30°C, and adding at least two equivalents of aqueous alkali metal hydroxide (MOH) and isolating the dimetal salt of the formula

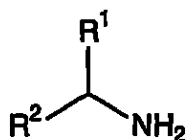


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- b. halogenating the dimetal salt with a halogenating reagent POX_3 , where X is Br or Cl to obtain the halogenated product of the formula



- c. reacting the halogenated product with an amine



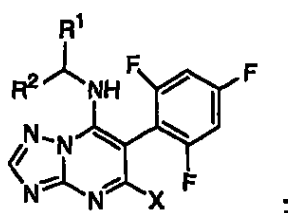
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- in an aprotic solvent from about 20°C to about 30°C to obtain the amine product of the formula

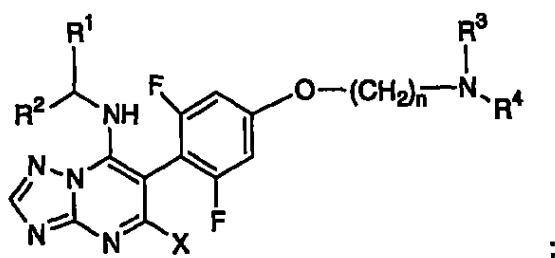
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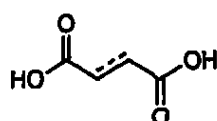
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- d. reacting an alkali metal hydride with an aminoalcohol $\text{HO}-(\text{CH}_2)_n-\text{NR}^3\text{R}^4$ for about 30 minutes in tetrahydrofuran at about 10 to 40°C, adding the amine product
 5 and heating to about 55-60° C for about 12 to 20 h, to obtain the 6-[(substituted)phenyl]-triazolopyrimidine product

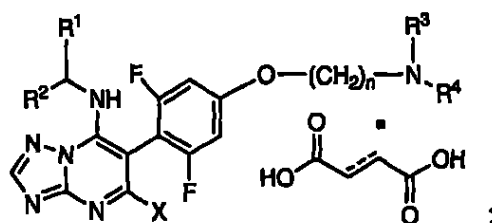


- e. reacting the 6-[(substituted)phenyl]-triazolopyrimidine product in water with a
 10 dicarboxylic acid of the formula



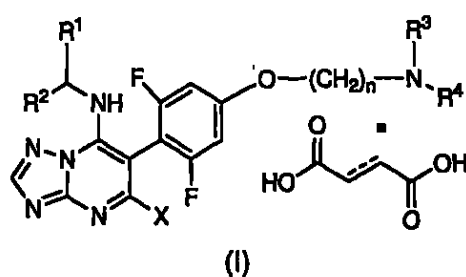
wherein the dashed line is an optional bond and adding a solvent selected from t-butylmethyl ether, ethyl acetate and toluene, to obtain the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt as a solid

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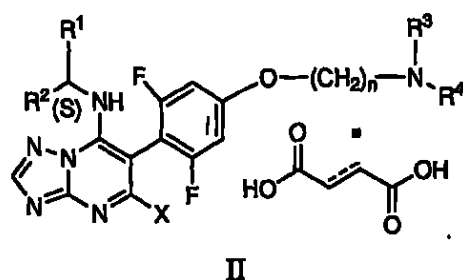
- f. crystallizing the 6-[(substituted)phenyl]- triazolopyrimidine dicarboxylic acid salt from water and collecting the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt;
- g. forming the anhydrous 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt by drying the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt; and
- h. treating the anhydrous 6-[(substituted)phenyl]- triazolopyrimidine dicarboxylic acid salt with water to obtain a 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt of formula (I) as a hydrated salt

10



- Especially preferred is a process for preparing a 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt and as a hydrated salt of formula (II)

15



20 wherein:

R¹ is CF₃ or C₂F₅;R² is H or C₁-C₃ alkyl;

n is an Integer of 2, 3, or 4;

X is Cl ;

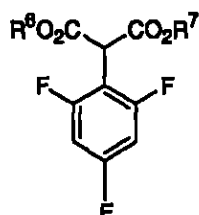
25 R³ and R⁴ are each independently H or C₁-C₃ alkyl;

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wherein the dotted line is an optional bond,
which process comprises

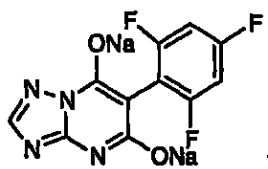
a. reacting a malonic acid ester of the formula



5

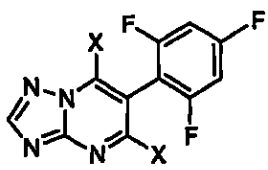
where R^6 and R^7 are independently C_1 - C_3 alkyl with 3-amino-1,2,4-triazole, in a mole ratio of about 1:1 in the presence of tributylamine and heating at about 130-170° C for about 1-6 h, cooling to about 130° C, diluting with toluene, cooling to about 20-30°C, and adding at least two equivalents of aqueous sodium hydroxide and isolating the disodium salt of the formula

10

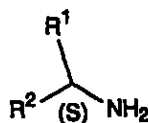


b. halogenating the disodium salt with a halogenating reagent POX_3 where X is Cl by heating to reflux for about 16 h to obtain the halogenated product of the formula

15

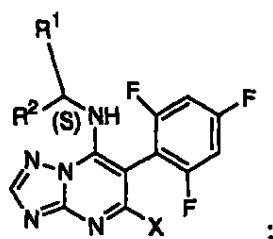


c. reacting the halogenated product with an amine

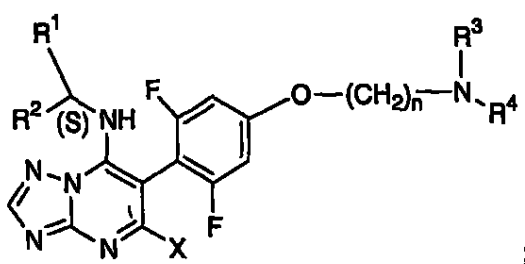


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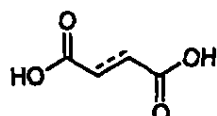
in an aprotic solvent from about 20°C to about 30°C for about 18-24 hours to obtain an amine product of the formula



- d. reacting an alkali metal hydride with an aminoalcohol $\text{HO}-(\text{CH}_2)_n-\text{NR}^3\text{R}^4$
 5 for about 30 minutes in tetrahydrofuran at about 20-30°C, adding the amine product
 and heating to about 55-60° C for about 14-16 hours to obtain the 6-
 [(substituted)phenyl]- triazolopyrimidine product

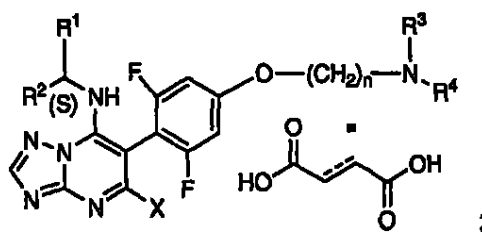


- 10 e. reacting the 6-[(substituted)phenyl]- triazolopyrimidine product in water with a
 dicarboxylic acid of the formula

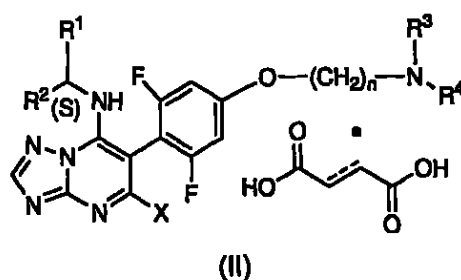


wherein the dashed line is an optional bond and adding t-butylmethyl ether to obtain
 the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt as a solid

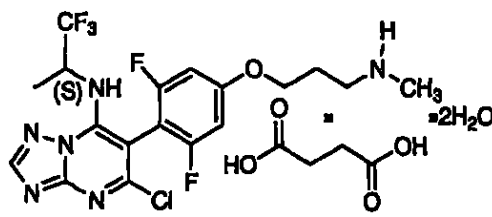
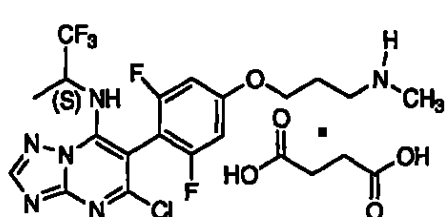
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- f. crystallizing the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt from water and collecting the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt;
- 5 g. forming the anhydrous 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt by drying the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt; and
- h. treating the anhydrous 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt with water in a saturated water atmosphere to obtain a 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt as a hydrated salt of formula (II)
- 10



- A particular embodiment of the invention
- 15 comprises an effective and efficient process for the preparation and purification of the succinate salt of [5-chloro-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-((1S)-2,2,2-trifluoro-1-methyl-ethyl)-amine of formula (A) and especially as the dihydrated form (B).



20

In a further more preferred embodiment, R^3 and R^4 are each independently H or C_1-C_3 alkyl.

In an additionally preferred embodiment, R^3 is H and R^4 is methyl.

The compounds prepared by the process of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to stereoisomers, such as enantiomers and diastereomers. The stereoisomers of the instant invention are
 5 named according to the Cahn-Ingold-Prelog System. While shown without respect to stereochemistry in Formula (I), the present invention includes all the individual possible stereoisomers; as well as the racemic mixtures and other mixtures of R and S stereoisomers (scalemic mixtures which are mixtures of unequal amounts of enantiomers) and pharmaceutically acceptable salts thereof. Included in the scope
 10 of the present invention are (*R*) and (*S*) isomers of compounds of general formula (I) having a chiral center and the racemates thereof. The present invention encompasses all stereoisomers of the compounds whether free from other stereoisomers or admixed with other stereoisomers in any proportion and thus includes, for instance, racemic mixture of enantiomers as well as the diastereomeric
 15 mixture of isomers. The absolute configuration of any compound may be determined by conventional X-ray crystallography.

DEFINITIONS

20

The term alkyl means a straight or branched alkyl of 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms.

Halogenating agent, means a brominating or chlorinating agent POX₃ wherein X is Br or Cl, preferably phosphorus oxybromide or phosphorus oxychloride.

25

Aprotic solvent includes as a solvent N,N-dimethylformamide.

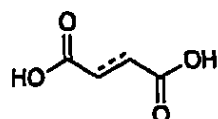
Alkali metal hydride includes lithium, potassium or sodium hydride.

The term alkali metal hydroxide includes potassium or sodium hydroxide, preferably about 50% aqueous sodium hydroxide.

Trialkylamine base includes tributylamine and tripropylamine.

30

Dicarboxylic acid means an acid of the formula



where the dotted line is an optional bond. Exemplary dicarboxylic acids include succinic acid and fumaric acid.

The term hydrated salt means a dicarboxylic acid salt of Formula (I) or (II) with bound water, wherein up to five moles of water or a fraction of whole moles (ie 2.5 moles)
 5 may be bound, preferably two moles of water as the dihydrate.

DETAILED DESCRIPTION OF THE INVENTION

In the new process for the preparation of 6-
 10 [(trisubstituted)phenyl]triazolopyrimidine compounds as described in Scheme 1, 2-(2,4,6-trifluoro-phenyl)-malonic acid diester 1 is reacted with 3-amino-1,2,4-triazole in a mole ratio of about 1:1 in the presence of a trialkylamine base, preferably tributylamine at a temperature range of about 130° to about 170°C, preferably at about 150° C for a time of about 1 to 6 h, preferably in the range of about 2 to about
 15 3 h. The reaction mixture on cooling to about 130° C is taken into toluene and treated with at least 2 equivalents of alkali metal hydroxide, preferably sodium hydroxide as a solution and more preferred as a solution of about 50% aqueous sodium hydroxide, in a temperature range of about 10 °C to 50 °C and stirring for about 1 to 3 h preferably from about 20°C to about 30°C, preferably about 25°C,
 20 forming a solid. The resulting solid is filtered, washed with toluene and dried at about 80°C under vacuum to give disodium salt of 6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-5,7-diol 2, in quantitative yield with a purity of >95% by high pressure liquid chromatography (HPLC).

In the second step of the above process, to the isolated disodium salt of 6-
 25 (2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-5,7-diol 2 over a time of about 20 to about 60 minutes preferably about 30 minutes is added a halogenating agent, preferably a brominating or chlorinating agent POX₃ wherein X is Br or Cl, preferably phosphorus oxybromide or phosphorus oxychloride in a ratio of 2 – 8 mL/g of disodium salt of 6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-5,7-diol and
 30 heated to reflux for about 8 to about 24 h, preferably about 16 h. The volatiles are removed by distillation to a residue which is distilled with toluene at least two times to afford a residue. The residue is dissolved in a solvent selected from ethyl acetate, dichloromethane or toluene and poured into water while maintaining the temperature

between about 5-15° C. The solvent is separated, washed with water then dried over sodium sulfate. The volatiles are removed by distillation to a residue which is dissolved in isopropyl alcohol and the volatiles again removed by distillation to provide a residue. The residue is dissolved in isopropyl alcohol and heated to about
5 40 to 82°C, preferably about 60° C, filtered, cooled to about 0°C over about an hour, continued cooling for about an additional two hours and the product collected by filtration and dried further at about 45°C to give 5,7-dihalo-6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]-pyrimidine 3 in a purity of >95% as shown by high pressure liquid chromatography (HPLC). Preferably, when phosphorous oxychloride is the
10 halogenating agent, 5,7-dichloro-6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]-pyrimidine is formed.

In the third step of the process, to a solution of 5,7-dihalo-6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]-pyrimidine 3 in an aprotic solvent, preferably anhydrous N,N-dimethylformamide (DMF), wherein the ratio of 5,7-dihalo-6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]-pyrimidine to DMF is about 3-10 mL DMF/g,
15 preferably 4 - 5 mL/g, is added an amine $R^1R^2CHNH_2$ 4 where R^1 and R^2 are hereinbefore defined, wherein the mole ratio of 5,7-dihalo-6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]-pyrimidine 3 to $R^1R^2CHNH_2$ 4 is in the range of about 1:2 – 1:3, preferably 1:2.5, with stirring at about 20-30°C for about 24 to 48 h, preferably about
20 24 hours. The reaction mixture is poured into cold water of about 10-20°C wherein the volume ratio of DMF to water is about 1:1 to 1:5, preferably about 1:3. Following about 30 minutes of additional stirring the product is collected by filtration washed with water and dissolved in isopropyl alcohol, cooled to about 0°C over about an hour, stirred for about an additional hour, collected by filtration and dried to give
25 amine 5. Preferably, 5,7-dichloro-6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]-pyrimidine in anhydrous N,N-dimethylformamide (DMF) is treated with preferred amine (S)-2,2,2-trifluoro-1-methyl-ethylamine at about 20-30°C for about 24 h and the reaction mixture is added slowly to cold water forming a precipitated solid product. The solid product is filtered, washed with water, and dried to give a crude
30 product. The crude product is crystallized from a mixture of isopropyl alcohol (IPA) and water to give the product in 82% yield and having a 98% HPLC purity and an enantiomeric excess of >99%.

In the fourth step of the process, to a suspension of alkali metal hydride preferably sodium hydride (80% in mineral oil) in anhydrous tetrahydrofuran is added amino alcohol $\text{HO}-(\text{CH}_2)_n-\text{NR}^3\text{R}^4$ 6 dropwise over about 10 to about 40 °C preferably at ambient temperature for about 30 minutes wherein the ratio of

5 tetrahydrofuran to aminoalcohol is about 6.5 mL THF/g aminoalcohol. A solution of amine 5 in tetrahydrofuran is added over about 10 to about 30 minutes, wherein the ratio of THF to amine is about 1 mL THF/g. The mixture is heated to about 55-80° C for about 12 to about 20 h, preferably about 16 h then cooled to about 0-8°C. To the reaction mixture is added water at about 5 to about 15 °C, preferably at about 10°C

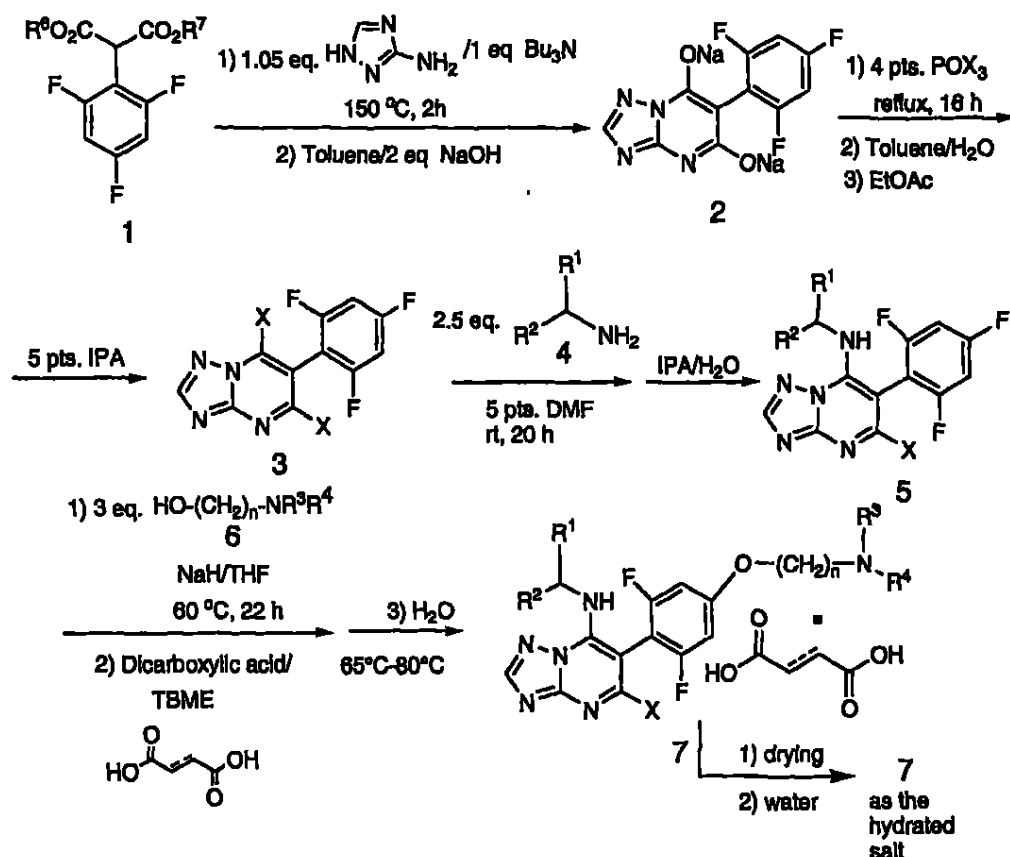
10 water in a ratio of about 10 mL water/ 1 g of amine. The volatiles are removed by distillation to afford a residue which is extracted with a solvent selected from t-butylmethyl ether (TBME), ethyl acetate and toluene and the aqueous phase separated. Dicarboxylic acid, preferably succinic acid (about 6.6 equivalents) is added to the separated aqueous solution and to the aqueous solution is further

15 added a solvent selected from t-butylmethyl ether (TBME), ethyl acetate and toluene and the mixture cooled to about 0° to about 10°C, preferably about 3°C. The solid precipitate is collected by filtration, washed with cold water then preferably TBME and the solid precipitate is dissolved at about 65° to about 80° in water and is crystallized from water, 10 ml water/g of solid precipitate to afford 6-

20 [(substituted)phenyl]- triazolopyrimidine 7 as the pharmaceutically acceptable dicarboxylic acid salt, preferably the succinic acid salt. When 6-[(substituted)phenyl]- triazolopyrimidine 7 as the pharmaceutically acceptable dicarboxylic acid salt, preferably the succinic acid salt and more preferably as the anhydrous salt is treated with a saturated atmosphere of (80-100%) relative humidity of water the hydrated salt

25 and in particular the dihydrated salt of 6-[(substituted)phenyl]-triazolopyrimidine] is formed.

Scheme 1:



Preferably, coupling of [5-chloro-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-((1*S*)-2,2,2-trifluoro-1-methyl-ethyl)-amine with 3-methylamino-propan-1-ol forms [5-Chloro-6-[2,6-difluoro-4-(3-methylamino-propoxy)-phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-((1*S*)-2,2,2-trifluoro-1-methyl-ethyl)-amine in the presence of alkali metal hydride, sodium hydride (NaH), in tetrahydrofuran (THF).

In a typical experiment, to a suspension of sodium hydride (NaH) in THF is added dropwise 3-methylamino-propan-1-ol at ambient temperature and the mixture stirred for about 30 min. A solution of [5-Chloro-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-((1*S*)-2,2,2-trifluoro-1-methyl-ethyl)-amine in THF is slowly added. The mixture is heated to about 60 °C and stirred for about 20 h, then cooled to 0 °C. Water is added dropwise while maintaining the temperature at about 10 ± 3 °C. The THF is removed by distillation to a residue. The residue is extracted with *t*-butylmethyl ether (TBME) and to the aqueous phase is added the dicarboxylic acid, in particular succinic acid (6.6 eq.) followed by the addition of

TBME. The mixture is cooled to about 3 ± 3 °C and the resulting precipitated solid product is filtered, washed with cold water and TBME. The wet solid at about 65°C to about 80°C is dissolved in water and is crystallized to give pure compound in 78% yield and having >99% HPLC purity and an enantiomeric excess of >99% which is dried under vacuum at about 35°C to about 40°C to afford the anhydrous salt which is treated with a saturated water atmosphere to afford the hydrated salt.

Optionally, in the salt formation of {5-Chloro-6-[2,6-difluoro-4-(3-methylamino-propoxy)-phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl}-((1S)-2,2,2-trifluoro-1-methyl-ethyl)-amine with succinic acid, fumaric acid may optionally replace the succinic acid to form the fumarate salt.

The following examples are presented to illustrate certain embodiments of the present invention, but should not be construed as limiting the scope of this invention.

Example 1

Disodium salt of 6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-5,7-diol

A mixture of 2-(2,4,6-trifluoro-phenyl)-malonic acid diethyl ester (400 g, 1.38 mol), 3-amino-1,2,4-triazole (122 g, 1.45 mol) and tributylamine (255 g, 1.38 mol) is heated to about 150 °C and stirred for about 2 h. The mixture is cooled to about 130 °C and the heating source is removed. Toluene (1600 mL) is then added over 30 min. The mixture is cooled to room temperature and sodium hydroxide solution (50%, 220 g, 2.76 mol) is added over about 15 min. The mixture is stirred for about 1 h from about 20°C to about 30°C. The solid is filtered and washed with toluene (2x600 mL) and dried at 80 °C/10mmHg for 40 h to give a white solid (470 g, 105%, >95%HPLC area purity), which is used directly in the next step.

Example 2

5,7-dichloro-6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine

To phosphorus oxychloride (1900 mL) is added disodium salt of 6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-5,7-diol (470 g, 1.38 mol) in portions over about 30 min. The mixture is heated to reflux for about 16 h. The solvent is removed by distillation to a residue and the residue distilled with toluene (2x500 mL). Then, the residue is dissolved into ethyl acetate (1000 mL) and the resulted mixture is poured into water (3000 g) while maintaining the temperature between 5 - 15 °C.

10 The organic phase is separated. The combined organic phase is washed with water (1000 mL) and dried over Na₂SO₄. After most of the solvent is removed by distillation, IPA (2x 500 mL) is added and distillation continued to a residue. The residue is dissolved in IPA (2350 mL) and heated to about 60 °C. The mixture is filtered at 50 - 60 °C and the filtrate is cooled to about 0 °C over about 1 h and

15 stirred for about another 2 h. The solid is filtered and dried at 45 °C/10 mmHg for 24 h to give a tan solid (243 g, 57%, 96% HPLC area purity).

Example 3

[5-Chloro-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-((1S)-2,2,2-trifluoro-1-methyl-ethyl)-amine

20

To a solution of 5,7-dichloro-6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine (200 g, 0.627 mol) in anhydrous DMF (1000 mL) is added (S)-2,2,2-trifluoro-1-methyl-ethylamine (177 g, 1.57 mol). The solution is stirred from about

25 20°C to about 30°C for 24 h. The reaction mixture is added to cold water (3000 mL) slowly over 30 min. The mixture is stirred for 30 min at 10 - 20 °C. The solid product is filtered and washed with water (2x 500 mL). The crude product is dissolved into IPA (1000 mL) at 50 °C. Water (2000 mL) is added to precipitate the product over 30 min. The mixture is cooled to 0 °C over 1 h and stirred for 1 h at this temperature.

30 The solid is filtered and dried at 65 °C/10 mmHg for 20 h to give a light yellow solid (204 g, 82%, 98% HPLC area purity and 99% ee).

Example 4

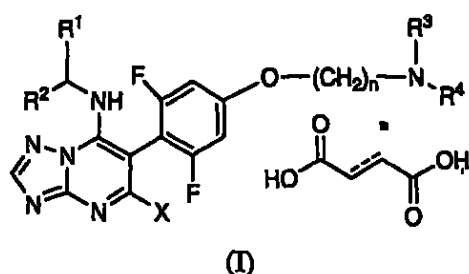
5-Chloro-6-(2,6-difluoro-4-[3-(methylamino)propoxy]phenyl)-N-[(1*S*)-2,2,2-trifluoro-1-methylethyl][1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine succinate salt dihydrate

- 5 To a suspension of NaH (40.9 g, 1.02 mol, 60% in oil) in anhydrous THF (750 mL) is added 3-methylamino-propan-1-ol (115 g, 1.21 mol) at about 20-30°C dropwise over 30 min. The mixture is stirred for 30 min. Then, a solution of [5-chloro-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-yl]-((1*S*)-2,2,2-trifluoro-1-methyl-ethyl)-amine (150 g, 0.379 mol) in THF (150 mL) is added slowly
- 10 over 15 min. The mixture is heated to 60 °C and stirred for 16 h, then cooled to 0 - 6 °C. Cold water (1500 mL) is added dropwise while maintain the temperature between 10 ± 3 °C. THF is removed by distillation. The reaction mixture is extracted with *t*-butylmethyl ether (TBME, 2x1000 mL) and to the separated aqueous phase is added in portions succinic acid (296 g, 2.51 mol) is added in portions and followed by
- 15 addition of TBME (1000 mL). The mixture is cooled to 3 ± 3 °C and stirred for 1 h. The crude solid product is filtered, washed with cold water (150 mL) and TBME (2x400 mL). The wet solid is dissolved into water (2000 mL) at about 75 °C. The solution is filtered at 60 - 70 °C and cooled to 0 °C over 1 h and stirred for 1 h at this temperature. The solid is filtered and dried at 35 °C/10 mmHg for 20 h to give a
- 20 white solid in anhydrous form (175 g, 80%, >99% HPLC area purity and 99%ee). A small portion of the anhydrous compound is placed in a drying dish of 80% - 100% relative humidity at about 20°C to about 30°C for 24 h. It absorbed 5.8%wt of water and stopped. This dihydrate is stable at about 20°C to about 30°C and at 5% -100% relative humidity. ¹H NMR (CDCl₃): δ 10.2 (bs, 1H), 8.26 (s, 1H), 6.80 (d, 2H, *J* =
- 25 10.5 Hz), 5.79 (m, 1H), 4.13 (t, 2H, *J* = 6.3 Hz), 3.03 (t, 2H, *J* = 7.2 Hz), 2.57 (s, 3H), 2.35 (s, 4H), 2.07 (m, 2H), 1.27 (d, *J* = 6.0, 3H).

CLAIMS:

1. A process for the preparation of a 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt and as a hydrated salt having the structural formula (I)

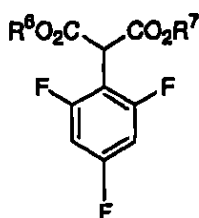
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wherein:

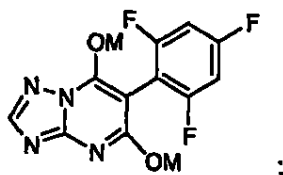
- 10 R^1 is CF_3 or C_2F_5 ;
 R^2 is H or C_1-C_3 alkyl;
 n is an integer of 2, 3, or 4;
 X is Cl or Br;
 R^3 and R^4 are each independently H or C_1-C_3 alkyl; or
15 R^3 and R^4 when optionally taken together with the nitrogen atom to which each is attached form a 4 to 6 membered saturated heterocyclic ring having 1-2 nitrogen atoms and 0-1 oxygen atoms or 0-1 sulfur atoms, and optionally substituted with R^5 ;
 R^5 is C_1-C_3 alkyl; wherein the dotted line is an optional bond,
which process comprises:

- 20 a. reacting a malonic acid ester of the formula



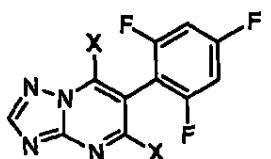
- 25 where R^6 and R^7 are independently C_1-C_3 alkyl with 3-amino-1,2,4-triazole, in the presence of trialkyl amine base and heating at about 130-170°C, for about 1 to 6 h, cooling to about 130° C, diluting with toluene, cooling to about 20°C to about 30°C,

and adding at least two equivalents of aqueous alkali metal hydroxide (MOH) and isolating the dimetal salt of the formula



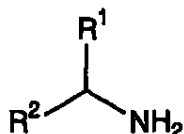
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b. halogenating the dimetal salt with a halogenating reagent POX_3 where X is Br or Cl to obtain the halogenated product of the formula



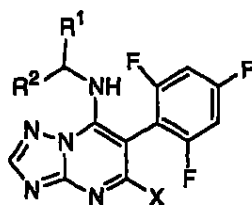
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c. reacting the halogenated product with an amine



15

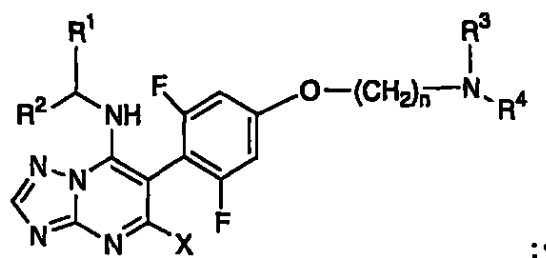
in an aprotic solvent at about 20°C to about 30°C to obtain the amine product of the formula



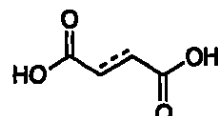
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d. reacting an alkali metal hydride with an aminoalcohol $\text{HO}-(\text{CH}_2)_n-\text{NR}^3\text{R}^4$ for about 30 minutes in tetrahydrofuran at about 10 to 40°C, adding the amine

product and heating to about 55-60° C for about 12 to 20 h, to obtain the 6-[(substituted)phenyl]-triazolopyrimidine product

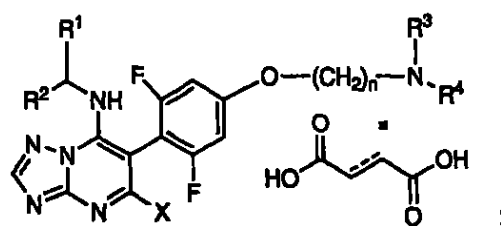


- 5 e. reacting the 6-[(substituted)phenyl]-triazolopyrimidine product in water with a dicarboxylic acid of the formula



wherein the dashed line is an optional bond and adding a solvent selected from t-butylmethyl ether, ethyl acetate and toluene to obtain the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt as a solid

10

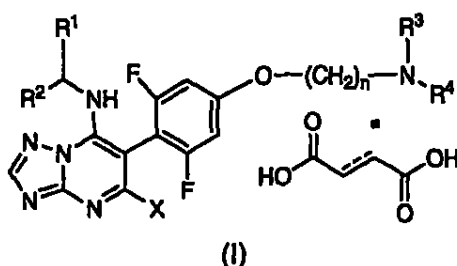


- 15 f. crystallizing the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt from water and collecting the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt;

- g. forming the anhydrous 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt by drying the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt;
- 20 and

h. treating the anhydrous 6-[(substituted)phenyl]- triazolopyrimidine dicarboxylic acid salt with water to obtain a 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt of formula (I) as a hydrated salt

5



- 10 2. A process according to claim 1 wherein the trialkylamine base is selected from tributylamine and tripropylamine.
3. A process according to claim 1 or claim 2 wherein the mole ratio of malonic acid ester to 3-amino-1,2,4-triazole is about 1:1.
- 15 4. A process according to any one of claims 1 to 3 wherein the alkali metal hydroxide is sodium hydroxide.
5. A process according to claim 4 wherein the alkali metal hydroxide, sodium hydroxide is about a 50% aqueous solution.
- 20 6. A process according to any one of claims 1 to 5 wherein the halogenating reagent is phosphorous oxychloride or phosphorous oxybromide.
- 25 7. A process according to claim 6 wherein the halogenating reagent is phosphorous oxychloride.
8. A process according to any one of claims 1 to 7 wherein the dicarboxylic acid is succinic acid or fumaric acid.

9. A process according to claim 8 wherein the dicarboxylic acid is succinic acid.
10. A process according to any one of claims 1 to 9 wherein the aprotic solvent is
5 N,N-dimethylformamide.
11. A process according to any one of claims 1 to 10 wherein R³ and R⁴ are each independently H or C₁-C₃ alkyl.
- 10 12. A process according to claim 11 wherein R³ is H and R⁴ is methyl.
13. A process according to any one of claims 1 to 12 wherein the heating in step a is at about 150°C for about 2 to 3 hours.
- 15 14. A process according to any one of claims 1 to 13 wherein the halogenating reagent in step b is heated to reflux for about 8 to 24 hours.
15. A process according to claim 14 wherein heating to reflux is for about 16 hours.
- 20 16. A process according to any one of claims 1 to 15 wherein the heating in step d is for about 16 hours.
17. A process according to any one of claims 1 to 16 wherein R¹ is CF₃ and R² is
25 methyl.
18. A process according to any one of claims 1 to 17 wherein the amine in step c has the (S) configuration

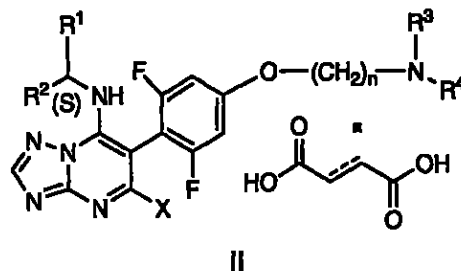


19. A process according to any one of claims 1 to 18 wherein the solvent in step e is t-butylmethyl ether.

5 20. A process according to any one of claims 1 to 19 wherein in step h the treating with water is by a saturated water atmosphere.

21. A process for the preparation of a 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt and as a hydrated salt of formula (II)

10



wherein:

R^1 is CF_3 or C_2F_5 ;

15 R^2 is H or C_1 - C_3 alkyl;

n is an integer of 2, 3, or 4;

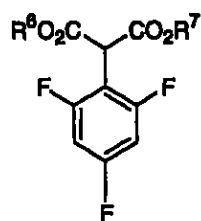
X is Cl ;

R^3 and R^4 are each independently H or C_1 - C_3 alkyl;

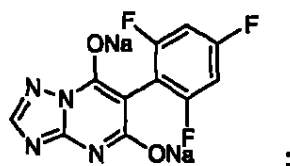
wherein the dotted line is an optional bond,

20 which process comprises

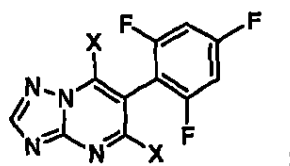
a. reacting a malonic acid ester of the formula



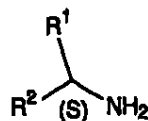
- where R⁶ and R⁷ are independently C₁-C₃ alkyl with 3-amino-1,2,4-triazole, in a mole ratio of about 1:1 in the presence of tributylamine and heating at about 150° C for about 1 to 6 h, cooling to about 130° C, diluting with toluene, cooling to about 20°C to about 30°C, and adding at least two equivalents of aqueous sodium hydroxide and isolating the disodium salt of the formula



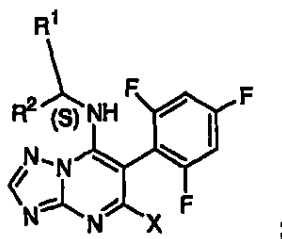
- b. halogenating the disodium salt with a halogenating reagent POX₃ where X is Cl by heating to reflux for about 16 h to obtain the halogenated product of the formula



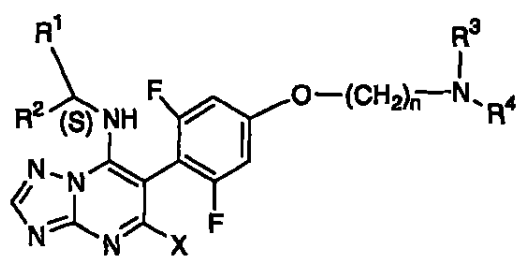
- c. reacting the halogenated product with an amine



in an aprotic solvent at about 20°C to about 30°C for about 24-48 hours to obtain an amine product of the formula

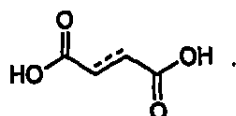


- d. reacting an alkali metal hydride with an aminoalcohol $\text{HO}-(\text{CH}_2)_n-\text{NR}^3\text{R}^4$ for about 30 minutes in tetrahydrofuran at ambient temperature, adding the amine product and heating to about 55-60° C for about 12-20 hours to obtain the 6-[(substituted)phenyl]- triazolopyrimidine product

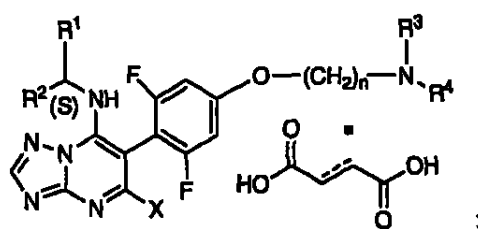


5

- e. reacting the 6-[(substituted)phenyl]- triazolopyrimidine product in water with a dicarboxylic acid of the formula



- 10 wherein the dashed line is an optional bond and adding t-butylmethyl ether to obtain the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt



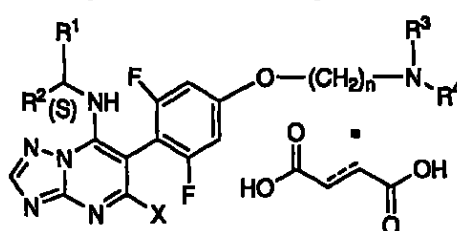
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- f. crystallizing the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt from water and collecting the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt;

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g. forming the anhydrous 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt by drying the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt; and

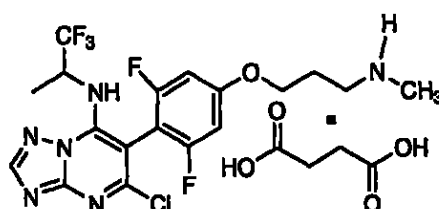
- 5 h. treating the 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt with water in a saturated water atmosphere to obtain a 6-[(substituted)phenyl]-triazolopyrimidine dicarboxylic acid salt as a hydrated salt of formula (II)



II

10

22. A process according to any one of claims 1 to 20 wherein

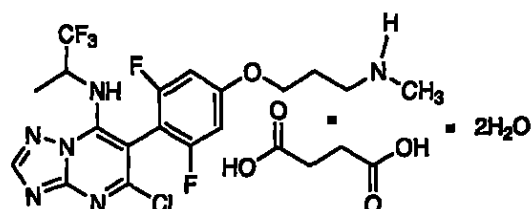


15

is produced.

23. A process according to any one of claims 1 to 20 wherein

20

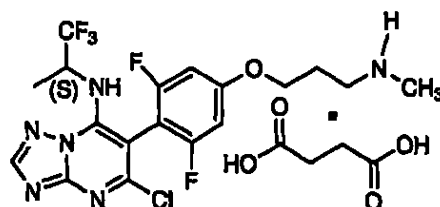


is produced.

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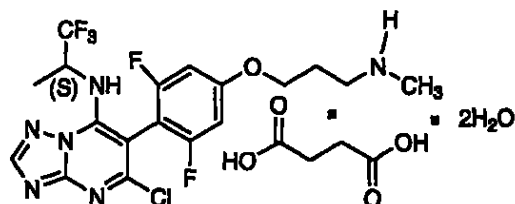
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24. A process according to claim 21 wherein



5 is produced.

25 A process according to claim 21 wherein



10 is produced.

26. A process according to any one of claims 1 to 22 wherein the mole ratio of halogenated product to amine in step C is about 1:2 to about 1:3.

PROCESO PARA LA PREPARACIÓN DE
INHIBIDORES DE TUBULINA

CAMPO DE LA INVENCION

La presente invención se relaciona con un proceso para la preparación de sales de ácido triazolopirimidino dicarboxílico que son inhibidores de tubulina útiles en el tratamiento de cáncer.

ANTECEDENTES DE LA INVENCION

Subsiste la necesidad en la técnica de agentes citotóxicos para uso en terapia de cáncer. En particular, subsiste la necesidad de agentes citotóxicos que inhiban o traten el crecimiento de tumores que tengan un efecto similar al paclitaxel e interfieren con el proceso de formación de microtúbulo. Adicionalmente, subsiste la necesidad en la técnica de agentes que aceleren la polimerización de tubulina y estabilicen los microtúbulos ensamblados.

Las drogas antimicrotúbulo son una categoría mayor de los agentes anticancer (Rowinsky, E., K. and, Tolcher A. W. Antimicrotubule agentes. In: V.T. Devita, Jr., S. Hellman, and S.A. Rosenberg (eds.), Cancer Principles and Practique, Ed. 6, pp. 431-452. Philadelphia: Lippicontt Williams and Wilkins, 2001). Las drogas antimicrotúbulo trabajan al interferir con la función de los microtúbulos celulares, particularmente el uso mitótico.

La irrupción de la función de huso normal conduce a la muerte celular apoptótica.

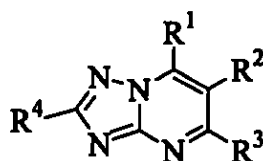
Muchos tumores son inherentemente resistentes (por ejemplo tumores del colon) a volverse resistentes después de muchos ciclos de tratamiento, al menos en parte debido a la expresión de transportadores de droga localizados en las membranas de la célula de cáncer que bombean las drogas hacia afuera de la célula y disminuyen de esta manera su eficacia (Gottesman, M.M Mechanisms of cancer drug resistance. Annu. Rev. Med., 53: 615-627, 2002). El mejor conocido de estos transportadores es la P-glicoproteína. De acuerdo con esto, subsiste necesidad de nuevos agentes con efectos similares a taxano sobre polimerización de microtúbulo que no sean sustratos de P-glicoproteína u otras de tales bombas y que por lo tanto solucionen esta causa de resistencia a taxano en pacientes.

Es una ventaja suministrar nuevos compuestos que provean un método para tratar o inhibir la proliferación celular, el crecimiento neoclásico y el crecimiento de tumores malignos en mamíferos al administrar compuestos que tengan actividad anticancerígena similar al paclitaxel. Es una ventaja adicional suministrar nuevos compuestos que provean un método para tratar o inhibir el crecimiento de tumores cancerígenos que expresen resistencia múltiple a la droga (MDR) o sean resistentes en razón del MDR. Es una ventaja adicional suministrar nuevos compuestos que provean un método para tratar o inhibir el crecimiento de tumores cancerosos en un mamífero con resistencia inherente o

adquirida a agentes quimioterapéuticos y en particular a agentes antimicóticos.

De acuerdo con esto, aunque se encuentran en desarrollo investigativo nuevos candidatos clínicos existe también una búsqueda de métodos nuevos y mejorados de preparación de aquellos candidatos clínicos seleccionados.

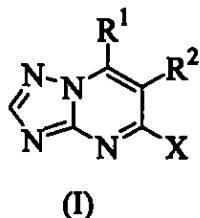
Se describe en la WO 02/02563 A2 el uso de triazolopirimidinas que tienen la fórmula estructural



En terapia de cáncer, y en particular como agentes de microtúbulo. Previamente descritas en las patentes U.S. números: 5,593,996; 5,756,509; 5,948,783; 5,981,534; 5,612,345; 5,994,360; 6,020,338; 5,985,883; 5,854,252; 5,808,066; 5,817,663; 5,955,252; 5,965,561; 5,986,153; 5,750,766; 6,117,876; 6,297,251; y Los Números de Publicación Internacional: WO 98/46607; WO98/46608; WO99/48893; WO99/41255; EPO 834513A2; EPO 782997A2; EPO 550113B1; FR2784381A1; EPO 989130A1; WO98/41496; WO94/20501; EPO 945453A1; EPO 562615A1; EP 077065 y EPO 562615B1 se encuentran los métodos de preparación y el uso de las triazolopirimidinas anteriores en agricultura como funguicidas.

Descrita en el caso sumario copendiente referencia No. AM 101270, número de solicitud 60/505,544, presentada en septiembre

24, 2003, una Serie de compuestos de triazolopirimidina de 6-[fenil (substituido)] que tienen la formula estructural



Que son inhibidores de microtúbulo y útiles en el tratamiento de cáncer.

A menudo, un proceso que trabaja en el laboratorio no es práctico para preparaciones a gran escala. En particular, la síntesis reportada de 5,7-dicloro-6-(fenil sustituido)-[1,2,4]triazolo[1,5a]pirimidino preparado mediante ciclización de dietil éster de ácido 2-(fenil sustituido)-malónico con 1-amino 2,3,5-triazol se describe en la US 6,117,876 y además se describe en la EP 0 770 615 A1 y la EP 0 770 615 B1 donde el 6-(fenil sustituido)-[1,2,4]triazolo[1,5-a]pirimidina-5,7-diol se forma y clorina mediante reacción con oxicloruro de fósforo para dar 5,7-dicloro-6-(fenil sustituido)-[1,2,4]triazol[1,5-a]pirimidina. Aunque las series descritas de etapas se pueden completar a una escala pequeña en un recipiente simple, la adición del reactivo clorinante, oxicloruro de fósforo a 130°C luego de remoción de etanol mediante oxidación, se dificulta para desarrollar preparaciones a gran escala. Además el proceso descrito anteriormente está limitado a síntesis a pequeña escala en razón a que el producto resultante como un aceite es difícil de purificar.

La US 5,986,135 y la US 6,117,876 describe un método para la preparación de [5-cloro-6-(fenilo sustituido)-[1,2,4]triazolo[1,5a]pirimidin-7-il] ((1S)-2,2,2,-trifluoro-1-metil-eti)-amina a través de aminación de 5,7-dicloro-6-(fenilo sustituido)-[1,2,4]triazolo[1,5-a]pirimidina con (S)-2,2,2-trifluoro-1-metil-etilamina. El método sin embargo no es completamente satisfactorio por que un aceite intermedio, que le falta un método practico de purificación, se forma cuando se prepara el 5,7-dicloro-6-(fenilo sustituido)-[1,2,4]triazolo[1,5-a]pirimidina y además se desarrolla la subsecuente reacción con (s)-2,2,2-trifluoro-1-metil-etilamina.

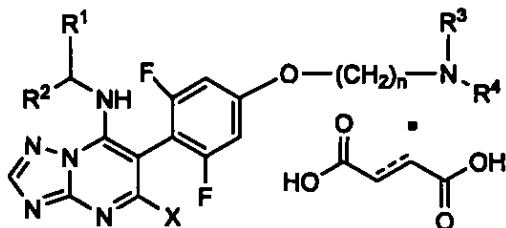
Claramente existe necesidad de suministrar un nuevo proceso para la preparación de los compuestos de triazolopirimidina 6-[fenilo(sustituido)] que solucione los inconvenientes de los procesos de la técnica anterior. En particular, subsiste necesidad de un proceso para preparar compuestos de triazolopirimidina 6[fenilo(sustituido)] cristalino purificado.

Subsisten adicionalmente necesidades de suministrar un nuevo proceso que en comparación con aquellos descritos en la técnica anteriormente mencionada que representen un avance significativo sobre el arte.

A la luz de la utilidad de los compuestos de triazolopirimidina en la terapia de cáncer, subsiste la necesidad de desarrollar métodos más simples y moderados para su preparación.

RESUMEN DE LA INVENCION

La presente invención suministra un proceso para la preparación de sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico y como una sal hidratada que tiene la formula estructural (1)



(I)

En donde:

R^1 es CF_3 o C_2F_5 ;

R^2 es H o alquilo C_1-C_3 ;

n es un entero de 2, 3 o 4;

X es Cl o Br;

R^3 y R^4 son cada uno independientemente H o alquilo C_1-C_3 ; o

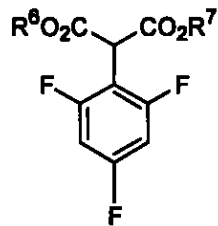
R^3 y R^4 cuando opcionalmente se toman juntos con el átomo de nitrógeno al cual ellos están unidos forman un anillo de heterocíclicos saturado de 4 a 6 miembros que tiene 1-2 átomos de nitrógeno y 0-1 átomos de oxígeno o 0-1 átomos de azufre, y opcionalmente sustituido con R^5 ;

R^5 es alquilo C_1-C_3 ;

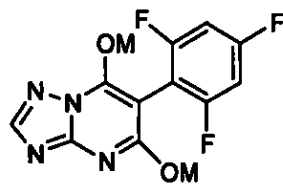
En donde la línea punteada es un enlace opcional,

Cuyo proceso comprende:

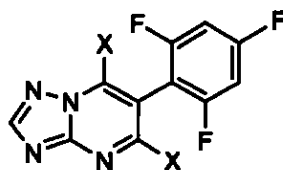
a. hacer reaccionar un éster de ácido malónico de la fórmula



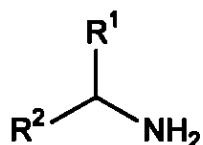
Donde R^6 y R^7 son independientemente alquilos C_1-C_3 con 3-amino-1,2,4-triazol en la presencia de base de trialquilamina y calentar a aproximadamente $130-170^\circ\text{C}$ durante aproximadamente 1 a 6 h, enfriando a aproximadamente 130°C , diluyendo con tolueno, enfriando desde aproximadamente 20°C a aproximadamente 30°C , y agregando al menos dos equivalentes de hidróxido de metal alcalino acuoso (MOH) y aislar la sal de bimetall de la fórmula



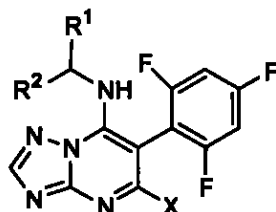
b. halogenar la sal de bimetall con un reactivo halogenante POX_3 donde X es Br o Cl para obtener el producto halogenado de la fórmula



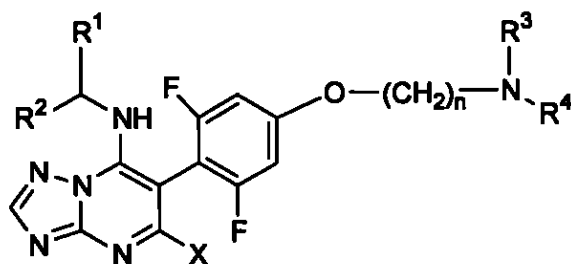
c. hacer reaccionar el producto halogenado con una amina



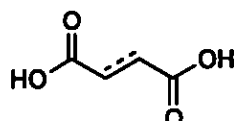
en un solvente aprótico desde aproximadamente 20° C a aproximadamente 30° C para obtener el producto de amina de la fórmula



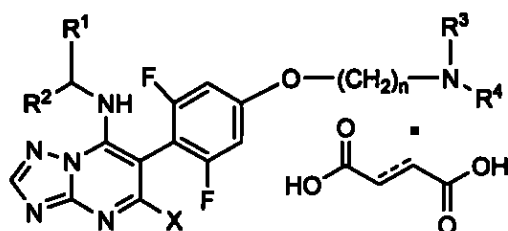
d. hacer reaccionar un hidruro de metal alcalino con un amino alcohol $\text{HO}-(\text{CH}_2)_n-\text{NR}^3\text{R}^4$ durante aproximadamente 30 minutos en tetrahidrofurano a aproximadamente 10 a 40° C, agregando el producto de amina y calentado a aproximadamente 55-60° C durante aproximadamente 12 a 20 h, para obtener el producto 6-[fenilo(sustituido)]-triazolopirimidina



e. hacer reaccionar el producto 6-[fenilo(sustituido)]-triazolopirimidina en agua con un ácido dicarboxílico de la fórmula



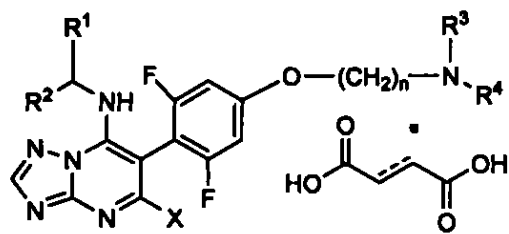
en donde la línea punteada es un enlace opcional al agregar un solvente seleccionado de t-butilmetil éter, etil acetato y tolueno, para obtener la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico como un sólido



f. cristalizar la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico de agua y reconectar en la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico;

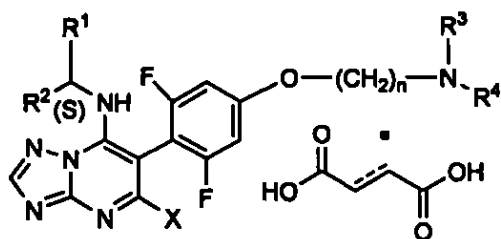
g. formar la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico anhidra al secar la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico;

h. tratar la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico con agua para obtener una sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico de fórmula (I) como una sal hidratada



(I)

Se prefiere especialmente un proceso para preparar una sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico y como una sal hidratada de fórmula (II)



II

En donde:

R¹ es CF₃ o C₂F₅;

R² es H o alquilo C₁-C₃;

n es un entero de 2, 3 o 4;

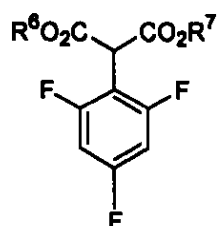
X es Cl;

R³ y R⁴ son cada uno independientemente H o alquilo C₁-C₂;

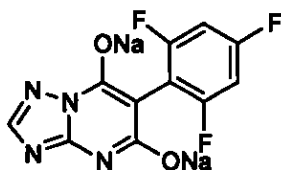
En donde la línea punteada es un enlace opcional;

Cuyo proceso comprende

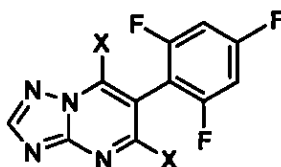
- a. hacer reaccionar un éster de ácido malónico de la fórmula



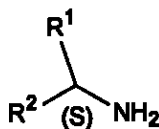
donde R^6 y R^7 son independientemente alquilos C_1-C_3 con -3-amino-1,2,4-triazol, en una proporción en mol de aproximadamente 1:1 en la presencia de tributilamina y calentado a aproximadamente $130-170^{\circ}\text{C}$ durante aproximadamente 1-6 h enfriando a aproximadamente 130°C diluyendo con tolueno, enfriando a aproximadamente $20-30^{\circ}\text{C}$, y agregando al menos dos equivalente de hidróxido de sodio acuoso y aislando la sal de disodio de la fórmula



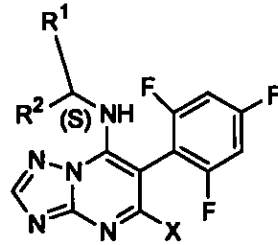
- b. halogenar la sal de disodio con reactivo halogenante POX_3 donde X es Cl al calentar a reflujo durante aproximadamente 16 h para obtener el producto halogenado de fórmula



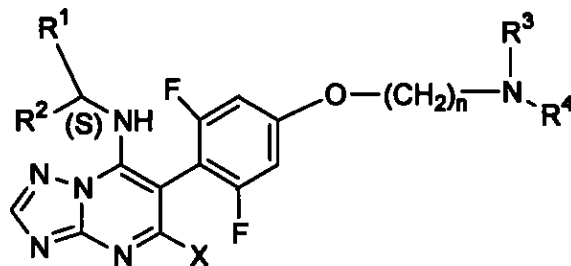
- c. hacer reaccionar el producto halogenado con una amina



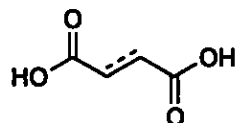
en un solvente aprótico desde aproximadamente 20° C a aproximadamente 30° C durante aproximadamente 18-24 horas para obtener un producto de amina de la fórmula



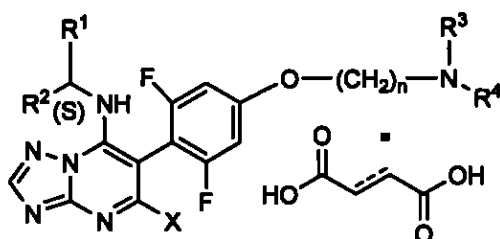
- d. hacer reaccionar un hidruro de metal alcalino con un amino alcohol $\text{HO}-(\text{CH}_2)_n-\text{NR}^3\text{R}^4$ durante aproximadamente 30 minutos en tetrahidrofurano a aproximadamente 20-30° C agregando el producto de amina y calentando a aproximadamente 55-60° C durante aproximadamente 14-16 horas para obtener el producto 6-[fenilo(sustituido)]-triazolopirimidina



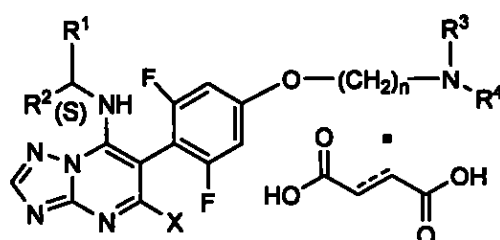
- e. hacer reaccionar el producto 6-[fenilo(sustituido)]-triazolopirimidina en agua con un ácido dicarboxílico de la fórmula



en donde la línea punteada es un enlace opcional y agregar t-butilmetil éter para obtener la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico como un sólido

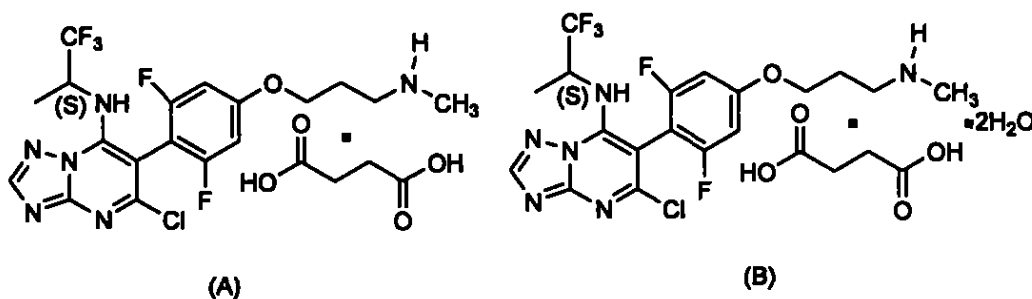


- f. la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico de agua y recolectar la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico;
- g. formar la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico al secar la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico;
y
- h. tratar la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico con agua en atmósfera de agua saturada para obtener una sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico como una sal hidratada (II)



(II)

Una modalidad particular de la invención comprende un proceso efectivo y eficiente para la preparación y purificación de la sal succinato de [5-cloro-6-(2,4,6-trifluoro-fenil)-[1,2,4]triazolo[1,5-a]pirimidina-7-il]-((1S)-2,2,2-trifluoro-1-metil-etil)-amina de la fórmula (A) y especialmente como la forma deshidratada (B)



En una modalidad más preferida adicional, R^3 y R^4 son cada uno independientemente H o alquilo C_1-C_3

En una modalidad preferida adicional R^3 es H y R^4 es metilo.

Los compuestos preparados por el proceso de esta invención pueden contener un átomo de carbono asimétrico y algunos de los compuestos de esa invención pueden contener uno o más centros asimétricos y pueden dar así origen a estereoisómeros, tales como enantiómeros y diastereómeros. Los estereoisómeros de la presente invención son denominados de acuerdo con el sistema Cahn-Ingold-Prelog. Aunque mostrados sin respecto a la estereoquímica la formula (I), la presente invención incluye todos los estereoisómeros posibles individuales; así como también las mezclas racémicas y otras mezclas de los estereoisómeros R y S (mezclas escalénicas que son mezclas de cantidades no iguales de enantiómeros) y sales farmacéuticamente aceptables de estas. Se

incluyen en el alcance de la presente invención los isómeros (R) y (S) de los compuestos de fórmula general (1) que tiene un centro quiral y los racematos de estos. La presente invención comprende todos los esteroisómeros de los compuestos sean libres de otros esteroisómeros o mezclados con otros esteroisómeros y en cualquier proporción e incluye así, por ejemplo, la mezcla racémica de enantiómeros así como también la mezcla diastereomérica de isómeros. La configuración absoluta de cualquier compuesto se puede determinar mediante cristalografía de rayos X convencional.

DEFINICIONES

El término alquilo significa un alquilo recto o ramificado de 1 a 4 átomos de carbono, preferiblemente 1 a 3 átomos de carbono.

El agente halogenante, significa un agente bromante o clorinante POX_3 , en donde X es Br o Cl, preferiblemente oxibromuro de fósforo u oxicloruro de fósforo.

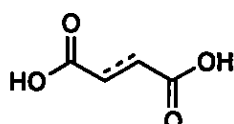
El solvente aprótico incluye como solvente N,N-dimetilformamida.

El hidruro de metal alcalino incluye litio, potasio o hidruro de sodio.

El término hidróxido de metal alcalino incluye hidróxido de potasio o sodio, preferiblemente aproximadamente y 50% hidróxido de sodio acuoso.

La base de etil alquilamina incluye tributilamina y tripropilamina.

Acido dicarboxílico significa un ácido de la fórmula



Donde la línea punteada es un enlace opcional. Los ácidos dicarboxílicos de ejemplo incluyen ácido succínico y ácido fumárico

El término sal hidratada significa una sal de ácido dicarboxílico de fórmula (I) o (II) con agua unida, donde hasta cinco moles de agua a una fracción de moles completas (es decir 2.5 moles) se pueden encontrar, preferiblemente dos moles de agua como el dihidrato.

DESCRIPCIÓN DETALLADA DE LA INVENCION

En el nuevo proceso de preparación de los compuestos 6-[fenilo(trisustituidos)]triazolopirimidina como se describió en el esquema 1, diéster de ácido 2-(2,4,6-trifluoro-fenil)-malónico 1 reacciona con 3-amino-1,2,4-triazol en una proporción en molde aproximadamente 1:1 en la presencia de base de trialquilamina preferiblemente tributilamina a una rango de temperatura de

aproximadamente 130° C a aproximadamente 170° C, preferiblemente a aproximadamente 150° C durante un tiempo de aproximadamente 1 a 6 h, preferiblemente en el rango de aproximadamente 2 a aproximadamente 3 h. la mezcla de reacción al enfriarse a aproximadamente 130° C es tomada en tolueno y tratada con al menos dos equivalentes de hidróxido de metal alcalino, preferiblemente hidróxido de sodio como una solución y más preferida como un solución de aproximadamente 50% de hidróxido de sodio acuoso, en un rango de temperatura de aproximadamente 10° C a 50 ° C y agitando durante aproximadamente 1 a 3 h preferiblemente desde aproximadamente 20°C a aproximadamente 30° C, preferiblemente aproximadamente 25° C, formando un sólido. El sólido resultante es filtrado, lavado con tolueno y secado a aproximadamente 80° C bajo vacío para dar sal de disodio de 6-(2,4,6-trifluorofenil)-[1,2,4]triazolo[1,5-a]pirimidina-5.7-diol 2, en rendimiento cuantitativo con una pureza >95% mediante cromatografía líquida de alta presión (HPLC).

En la segunda etapa del proceso anterior, la sal de disodio aislada de 6-(2,4,6-trifluorofenil)-[1,2,4]triazolo[1,5-a]pirimidina-5.7-diol 2 durante un tiempo de aproximadamente 20 a aproximadamente 60 minutos preferiblemente aproximadamente 30 minutos se agrega un agente halogenante preferiblemente un agente bromante o clorinante POX₃ en donde X es Br o Cl, preferiblemente oxibromuro de fósforo u oxibromuro de fósforo en una proporción de 2-8 mL/g de sal de disodio de 6-(2,4,6-trifluorofenil)-[1,2,4]triazolo[1,5-a]pirimidina-5.7-diol y calentada a reflujo durante 8 a 24 h, preferiblemente aproximadamente 16h. Los volátiles se remueven mediante destilación a un residuo que es

destilado con tolueno al menos dos veces para lograr un residuo. El residuo se disuelve en un solvente seleccionado de acetato de etilo, diclorometano o tolueno y se vierte en agua aunque manteniendo la temperatura entre aproximadamente 5-15° C. El solvente se separa, se lava con agua luego se seca sobre sulfato de sodio. Los volátiles son removidos mediante destilación a un residuo que es disuelto en alcohol isopropílico y los volátiles se remueven de nuevo mediante destilación para suministrar un residuo. El residuo se disuelve en alcohol isopropílico y se calienta a aproximadamente 40 a 82° C preferiblemente aproximadamente 60° C, se filtra, se enfría a aproximadamente 0° C durante aproximadamente una hora, se continua enfriando durante aproximadamente dos horas adicionales y el producto se recolecta mediante filtración y se seca adicionalmente a aproximadamente a 45° C para dar 5,7-dialo-6-(2,4,6-trifluorofenil)-[1,2,4]triazolo[1,5-a]-pirimidina 3 en una pureza >95% como se muestra mediante cromatografía líquida de alta presión (HPLC). Preferiblemente, cuando el oxicloruro de fósforo es el agente halogenante, si se forma 5,7-dicloro-6-(2,4,6-trifluorofenil)-[1,2,4]triazolo[1,5-a]-pirimidina.

En la tercera etapa del proceso, a una solución de 5,7-dialo-6-(2,4,6-trifluorofenil)-[1,2,4]triazolo[1,5-a]-pirimidina 3 en un solvente aprótico, preferiblemente N,N-dimetilformamida anhidra (DMF), en donde la proporción de 5,7-dialo-6-(2,4,6-trifluorofenil)-[1,2,4]triazolo[1,5-a]-pirimidina a DMF es aproximadamente 3-10 mL DMF/g, preferiblemente 4-5 mL/g, se agrega una amina $R^1R^2CHNH_2$ 4 donde R^1 y R^2 son como se definió anteriormente, en donde la proporción molar de 5,7-dialo-6-

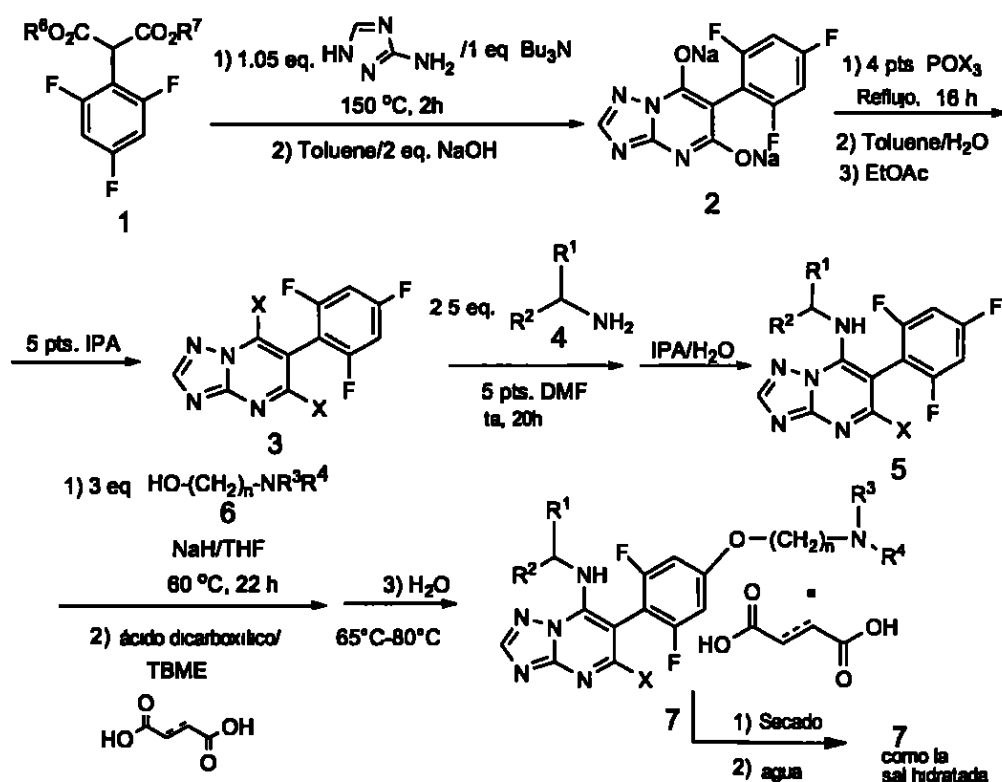
(2,4,6-trifluorofenil)-[1,2,4]triazolo[1,5-a]-pirimidina 3 a $R^1R^2CHNH_2$ 4 esta en el rango de aproximadamente 1:2-1:3, preferiblemente 1:2.5, con agitación a aproximadamente 20-30° C durante aproximadamente 24 h, preferiblemente aproximadamente 24 horas. La mezcla de reacción se vierte en agua fría de aproximadamente 10-20° C en donde la proporción en volumen de DMF agua es aproximadamente 1:1 a 1:5, preferiblemente aproximadamente 1:3. Luego de aproximadamente 30 minutos de agitación adicional el producto se recolecta mediante filtración se lava con agua y se disuelve en alcohol isopropílico, se enfría a aproximadamente 0° C durante aproximadamente una hora, se agita durante aproximadamente una hora adicional, se recolecta mediante filtración y se seca para dar la amina 5. Preferiblemente, 5,7-dicloro-6-(2,4,6-trifluorofenil)-[1,2,4]triazolo[1,5-a]-pirimidina en N,N-dimetilformamida anhidra (DMF) si se trata con la amina preferida (S)-2,2,2-trifluoro-1-metil-etilamina a aproximadamente 20-30° C durante aproximadamente 24 h y la mezcla de reacción se agrega lentamente para enfriar el agua formando un producto sólido precipitado. El producto sólido se filtra, se lava con agua y se seca para dar un producto crudo. El producto crudo se cristaliza de una mezcla de alcohol isopropílico (IPA) y agua para dar el producto el 82% de rendimiento y tener el 98% de pureza HPLC y un exceso en enantiomérico de >99%.

En la cuarta etapa del proceso, a una suspensión de hidruro de metal alcalino preferiblemente hidruro de sodio (60% en aceite mineral) en tetrahidrofurano anhidro se agrega amino alcohol $HO-(CH_2)_n-NR^3R^4$ 6 gota a gota durante aproximadamente 10 a aproximadamente 40° C preferiblemente a temperatura ambiente

durante aproximadamente 30 minutos en donde la proporción de tetrahidrofurano a amino alcohol es aproximadamente 605 mL THF/g amino alcohol. Una solución de amina 5 tetrahidrofurano se agrega durante aproximadamente 10 a 30 minutos, en donde la proporción de THF a amina es aproximadamente un mL THF/g. la mezcla se calienta a aproximadamente 55-60° C durante aproximadamente 12 a aproximadamente 20 h, preferiblemente aproximadamente 16 h luego se enfría a aproximadamente 0-6° C. a la mezcla de reacción se agrega agua a aproximadamente 5 a aproximadamente 15° C, preferiblemente a agua a aproximadamente 10° C en una proporción aproximadamente 10 mL agua/1 g de amina. Los volátiles son removidos mediante destilación para lograr un residuo que se extrae con un solvente seleccionado de t-butilmetil éter (TBME), etil acetato de tolueno y en la fase acuosa se separa. Se agrega ácido de carboxílico, preferiblemente ácido succínico (aproximadamente 6.6 equivalente) a la solución acuosa separada y la solución acuosa le es agregado adicionalmente un solvente seleccionado de t-butilmetil éter (TBME), etil acetato y tolueno y la mezcla se enfría a aproximadamente 0° C a aproximadamente 10° C, preferiblemente a aproximadamente 3° C. el precipitado sólido se recolecta mediante filtración, se lava con agua fría luego preferiblemente TBME y el precipitado sólido se disuelve a aproximadamente 65° a aproximadamente 80° en agua y se cristalizado del agua, 10 mL agua/g de sólido precipitado para lograr 6-[fenil(sustituido)]-triazolopirimidina 7 como la sal de ácido dicarboxílico farmacéuticamente aceptable, preferiblemente la sal de ácido succínico. Cuando 6-[fenil(sustituido)]-triazolopirimidina 7 como la sal de ácido de carboxílico farmacéuticamente aceptable, preferiblemente la sal de ácido

succínico y más preferiblemente como la sal anhidra se trata con una atmósfera saturada con humedad relativa (80-100%) de agua la sal hidratada y en particular se forma la sal dihidratada de 6-[fenilo(sustituido)]triazolopirimidina].

Esquema 1:



Preferiblemente, el acoplamiento de [5-cloro-6-(2,4,6-trifluoro-fenil)-[1,2,4]triazol[1,5,a]pirimidin-7-il]-((1S)-2,2,2-trifluoro-1-metil-etil)-amina con 3-metilamino-propan-1-ol forma {5-cloro-6-[2,6-difluoro-4-(3-metilamino-propoxi)-fenil]-[1,2,4]triazolo[1,5-a]pirimidin-7-il]-((1S)-2,2,2-trifluoro-1-metil-etil)-amina en la presencia de hidruro de metal alcalino, hidruro de sodio (NaH), en tetrahidrofurano (THF).

En un experimento típico, a una suspensión de hidruro de sodio (NaH) en THF se agrega gota a gota 3-metilamino-propan-1-ol a temperatura ambiente y la mezcla se agita durante aproximadamente 30 min. Una solución de {5-cloro-6-(2,4,6-trifluoro-fenil)-[1,2,4]triazol[1,5,a]pirimidin-7-il}-((1S)-2,2,2-trifluoro-1-metil-etil)-amina en THF se agrega lentamente. La mezcla se calienta a aproximadamente 60° C y se agita durante aproximadamente 20 h, luego se enfría a 0° C. se agrega agua gota a gota aunque manteniendo la temperatura a aproximadamente 10 ± 3° C. el THF se remueve mediante destilación a un residuo. El residuo se extrae con t-butilmetil éter (TBME) y se agrega a la fase acuosa el ácido dicarboxílico, en particular ácido succínico (606 eq.) seguido mediante la adición de TBME. La mezcla se enfría a aproximadamente 3 ± 3° C y el producto sólido precipitado resultante se filtra, se lava con agua fría y TBME. El sólido húmedo a aproximadamente 65° C a aproximadamente 80° C se disuelve en agua y se cristaliza para dar un compuesto puro con 78% de rendimiento y que tiene >99% de pureza HPLC y un exceso enantiomérico de >99% que es secado bajo vacío a aproximadamente 35° C a aproximadamente 40° C para lograr la sal anhidra que se trata con una atmósfera de agua saturada para lograr la sal hidratada.

Opcionalmente, en la formación de sal de {5-cloro-6-(2,6-difluoro-4-(3-metilamino-propoxi)-fenil)-[1,2,4]triazolo[1,5-a]pirimidin-1-il}-((1S)-2,2,2-trifluoro-1-metil-etil)-amina con ácido succínico, el ácido fumárico puede opcionalmente reemplazar el ácido succínico para formar la sal fumarato.

Los siguientes ejemplos se presentan para ilustrar ciertas modalidades de la presente invención, pero no se deben considerar como limitantes del alcance de la invención.

Ejemplo 1

Sal disodio de 6-(2,4,6-trifluorofenil)-[1,2,4]triazolo[1,5-a]pirimidina-5,7-diol

Una mezcla de dietil éster de ácido 2-(2,4,6-trifluorofenil)-malónico (400 g, 1.38 mol), 3-amino-1,2,4-triazol (122 g, 1.45 mol) y tributilamina (255 g, 1.38 mol) se calienta a aproximadamente 150° C y se agita durante aproximadamente 2 h. la mezcla se enfría a aproximadamente 130° C y se remueve la fuente de calentamiento. Se agrega entonces tolueno (1600 mL) durante 30 min. La mezcla se enfría a temperatura ambiente de cuarto y se agrega solución de hidróxido de sodio (50%, 220 g, 2.76 mol) durante aproximadamente 15 min. La mezcla se agita durante aproximadamente 1 h desde aproximadamente 20° C a aproximadamente 30° C. El sólido se filtra y se lava con tolueno (2 x 600 mL) y se seca a 80° C/10mmHg durante 40 h para dar un sólido blanco (470 g, 105%, >95% de pureza de área de HPLC), que se utiliza directamente en la siguiente etapa.

Ejemplo 2

5,7-dicloro-6-(2,4,6-trifluorofenil)-[1,2,4]triazolo[1,5-a]pirimidina

A oxidloruro de fósforo (1900 mL) se agrega sal disodio de 6-(2,4,6-trifluorofenil)-[1,2,4]triazolo[1,5-a]-pirimidina-5,7-diol (470 g, 1.38 mol) en porciones durante aproximadamente 30 min. La mezcla se calienta a reflujo durante aproximadamente 16 h. el solvente se remueve mediante destilación a un residuo y el residuo se destila con tolueno (2 x 500 mL). Y luego, el residuo se disuelve en acetato de etilo (1000 mL) y la mezcla resultante es vertida en agua (3000 g) aunque manteniendo la temperatura entre 5-15° C. se separa la fase orgánica. La fase orgánica combinada se lava con agua (1000 mL) y se seca sobre Na₂SO₄. Después la mayoría del solvente se remueve mediante destilación, IPA (2 x 500 mL) se agrega y se continúa la destilación a un residuo. El residuo se disuelve en IPA (2350 mL) y se calienta a aproximadamente 60° C. la mezcla se filtra a 50-60° C y el filtrado se enfría a aproximadamente 0° C durante a aproximadamente 1 h y se agita durante aproximadamente otras 2 h. el sólido se filtra y se seca a 45° C/10 mmHg durante 24 h para dar un sólido tostado (243 g, 57%, 96% de pureza de área HPLC).

Ejemplo 3

[5-cloro-6-(2,4,6-trifluoro-fenil)-[1,2,4]triazolo[1,5-a]pirimidin-7-il]-((1S)-2,2,2-trifluoro-1-metil-etil)-amina

A una solución de 5,7-dicloro-6-(2,4,6-trifluorofenil)-[1,2,4]triazolo[1,5-a]pirimidina (200 g, 0.627 mol) en DMF anhidro (1000 mL) se agrega (S)-2,2,2-trifluoro-1-metil-etilamina (177 g, 1.57 mol). La solución se agita desde aproximadamente 20° C a aproximadamente 30° C durante 24 h. la mezcla de reacción se

agrega a agua fría (3000 mL) lentamente durante 30 min. La mezcla se agita durante 30 min a 10-20° C. El producto sólido se filtra y se lava con agua (2 x 500 mL). El producto crudo se disuelve en IPA (1000 mL) a 50° C. se agrega agua (2000 mL) para precipitar el producto durante 30 min. La mezcla se enfría a 0° C durante 1 h y se agita durante 1 h a esa temperatura. El sólido se filtra y se seca a 65° C/10 mmHg durante 20 h para dar un sólido amarillo claro (204 g, 82%, 98% de pureza de área HPLC y 99%ee).

Ejemplo 4

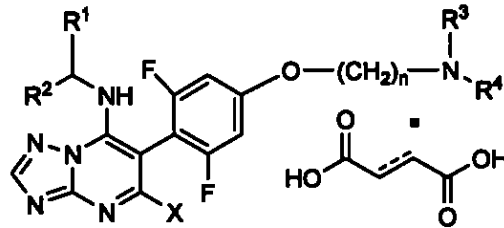
Sal dihidrato de 5-cloro-6-(2,6-difluoro-4-[3-(metilamino)propoxi]fenil)-N-[(1S)-2,2,2-trifluoro-1-metiletil][1,2,4]triazolo[1,5-a]pirimidin-7-amina succinato

A una suspensión de NaH (40.9 g, 1.02 mol, 60% en aceite) en THF anhidro (750 mL) se agrega 3-metilamino-propan-1-ol (115 g, 1.21 mol) a aproximadamente 20-30° C gota a gota durante 30 min. La mezcla se agita durante 30 min. Luego, una solución de [5-cloro-6-(2,4,6-trifluoro-fenil)-[1,2,4]triazolo[1,5-a]pirimidin-7-il]-((1S)-2,2,2-trifluoro-1-metil-etil)-amina (150 g, 0.379 mol) en THF (150 mL) se agrega lentamente durante 15 min. La mezcla se calienta a 60°C y se agita durante 16 h, luego se enfría a 0-6° C. Se agrega a gota agua fría (1500 mL) aunque manteniendo la temperatura entre 10 ± 3° C. El THF se remueve mediante destilación. La Mezcla de reacción se extrae con t-butilmetil éter (TBME, 2x1000 mL) y a la fase acuosa separada se agrega en porciones ácido succínico (296 g, 2.51 mol) se agrega en porciones y se sigue por la adición de TBME (1000 mL). La

mezcla se enfría a $3 \pm 3^{\circ} \text{C}$ y se agita durante 1 h. el producto sólido crudo se filtra, se lava con agua fría (150 mL) y TBME (2x400 mL). El sólido húmedo se disuelve en agua (2000 mL) a aproximadamente 75°C . la solución se filtra a $60\text{--}70^{\circ} \text{C}$ y se enfría 0°C durante 1 h y se agita durante 1 h a esta temperatura. El sólido se filtra y se seca a $35^{\circ} \text{C}/10 \text{ mmHg}$ durante 20 h para dar un sólido blanco en forma anhidra (175 g, 80%, >99% de pureza de área HPLC y 99% ee). Una pequeña porción del compuesto anhidro se ubica en un plato de secado de 80%–100% donde da relativa aproximadamente 20°C a aproximadamente 30°C durante 24 h. este absorbió 5.8% en peso de agua y se detuvo. Este dihidrato es estable a aproximadamente 20°C a aproximadamente 30°C y 5%–100% de humedad relativa. ^1H NMR (CDCl_3): δ 10.2 (bs, 1H), 6.80 (d, 2H, $J=10.5 \text{ Hz}$), 5.79 (m, 1H), 4.13 (t, 2H, $J=6.3 \text{ Hz}$), 3.03 (t, 2H, $J=7.2 \text{ Hz}$) 2.57 (s, 3H), 2.35 (s, 4H), 2.07 (m, 2H), 1.27 (d, $J=6.0$, 3H).

REIVINDICACIONES

1. Un proceso para la preparación de una sal de ácido 6-[fenil(sustituido)]-triazolpirimidina dicarboxílico y como una sal hidratada que tiene la formula estructural (I)



(I)

En donde:

R^1 es CF_3 o C_2F_5 ;

R^2 es H o alquilo C_1-C_3 ;

n es un entero de 2, 3 o 4;

X es Cl o Br;

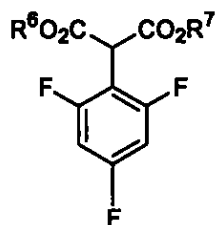
R^3 y R^4 son cada uno independientemente H o alquilo C_1-C_2 ; o

R^3 y R^4 cuando se toman opcionalmente juntos con el átomo de nitrógeno al cual cada uno esta unido forman un anillo heterocíclico saturado de 4 a 6 miembros que tiene 1-2 átomos de nitrógeno y 0-1 átomos de oxígeno o 0-1 átomos de azufre, y opcionalmente sustituido son R^5 ;

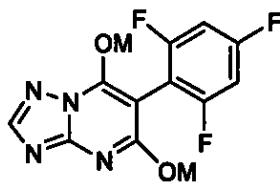
R^5 es alquilo C_1-C_3 ; en donde la línea punteada es un enlace opcional,

Cuyo proceso comprende:

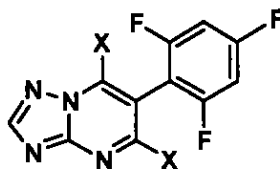
- a. hacer reaccionar un éster de ácido malónico de la fórmula



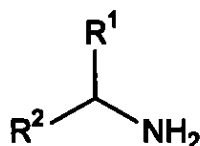
Donde R^6 y R^7 son independientemente alquilos C_1-C_3 con 3-amino-1,2,4-triazol, en la presencia de base de trialquil amina y calentando a aproximadamente $130-170^\circ C$, durante aproximadamente 1 a 6 h, enfriando a aproximadamente $130^\circ C$, diluyendo con tolueno, y enfriando a aproximadamente $20^\circ C$ a aproximadamente $30^\circ C$, y agregando al menos dos equivalentes de hidróxido de metal alcalino acuoso (MOH) y aislando la sal de dimetal de la fórmula



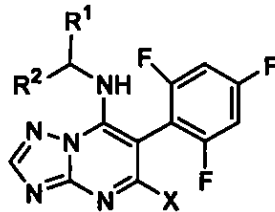
b. halogenar la sal de dimetal con un reactivo halogenante POX_3 donde X es Br o Cl para obtener el producto halogenado de la fórmula



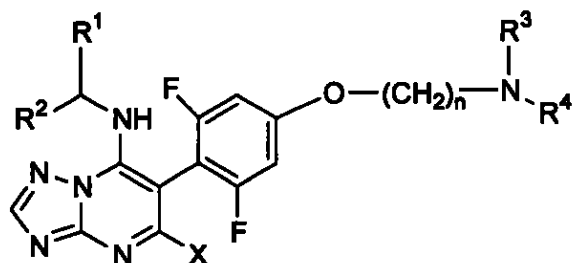
c. hacer reaccionar el producto halogenado con una amina



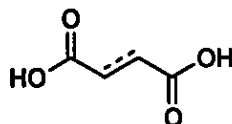
en un solvente aprótico a aproximadamente 20° C a aproximadamente 30° C para obtener el producto amina de la fórmula



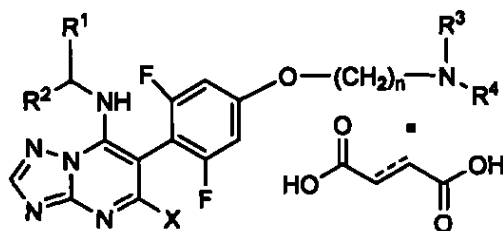
d. hacer reaccionar un hidruro de metal alcalino con un amino alcohol $\text{HO}-(\text{CH}_2)_n-\text{NR}^1\text{R}^4$ durante aproximadamente 30 minutos en tetrahidrofurano a aproximadamente 10 a 40° C, el producto de amina y calentando a aproximadamente 55-60° C durante aproximadamente 12 a 20 h para obtener el producto 6-[fenilo(sustituido)]-triazolopirimidina



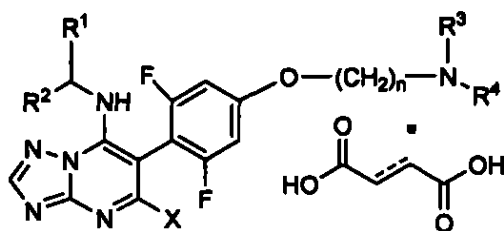
e. hacer reaccionar el producto 6-[fenilo(sustituido)]-triazolopirimidina en agua con un ácido de carboxílico de la fórmula



En donde la línea punteada es un enlace opcional y agregando un solvente seleccionado de t-butilmetil éter, etil acetato y tolueno para obtener la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico como un sólido



- f. cristalizar la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico de agua y recolectar la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico;
- g. formar la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico anhidra al secar la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico; y
- h. tratar la sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico con agua para obtener una sal de ácido 6-[fenilo(sustituido)]-triazolopirimidina dicarboxílico de fórmula (I) como una sal hidratada

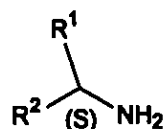


(I)

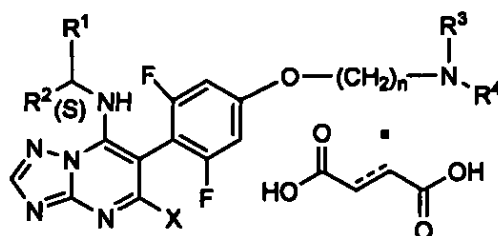
2. Un proceso de acuerdo a la reivindicación 1 en donde la base trialquilamina se selecciona de tributilamina y tripropilamina
3. Un proceso de acuerdo a la reivindicación 1 o reivindicación 2 en donde la proporción en molde de éster de ácido malónico a 3-amino-1,2,4-triazol es aproximadamente 1:1
4. Un proceso de acuerdo a una cualquiera de las reivindicaciones 1 a 3 en donde el hidróxido de metano alcalino es hidróxido de sodio
5. Un proceso de acuerdo a la reivindicación 4 en donde el hidróxido de metano alcalino, hidróxido de sodio es aproximadamente 50% de solución acuosa.
6. Un proceso de acuerdo a una cualquiera de las reivindicaciones 1 a 5 en donde el reactivo halogenante es oxicloruro de fósforo u oxibromuro de fósforo.
7. Un proceso de acuerdo a la reivindicación 6 en donde le reactivo halogenante es oxicloruro de fósforo.

8. Un proceso de acuerdo a una cualquiera de las reivindicaciones 1 a 7 en donde el ácido dicarboxílico es ácido succínico o ácido fumárico.
9. Un proceso de acuerdo a la reivindicación 8 en donde el ácido dicarboxílico es ácido succínico.
10. Un proceso de acuerdo a una cualquiera de las reivindicaciones 1 a 9 en donde el solvente aprótico es N,N-dimetilformamida.
11. Un proceso de acuerdo a una cualquiera de las reivindicaciones 1 a 10 en donde R^3 y R^4 son cada una independientemente H o alquilo C_1-C_3 .
12. Un proceso de acuerdo a la reivindicación 11 R^3 es y R^4 es metilo
13. Un proceso de acuerdo a una cualquiera de las reivindicaciones 1 a 12 en donde el calentamiento en la etapa a es aproximadamente $150^{\circ}C$ durante aproximadamente 2 a 3 horas.
14. Un proceso de acuerdo a una cualquiera de las reivindicaciones 1 a 13 en donde el reactivo halogenante en la etapa b se calienta a reflujo durante aproximadamente 8 a 24 horas.

15. Un proceso de acuerdo a la reivindicación 14 en donde el calentamiento a reflujo es durante aproximadamente 16 horas.
16. Un proceso de acuerdo a una cualquiera de las reivindicaciones 1 a 15 en donde el calentamiento en la etapa d es durante aproximadamente 16 horas.
17. Un proceso de acuerdo a una cualquiera de las reivindicaciones 1 a 16 en donde R^1 es CF_3 y R^2 es metilo.
18. Un proceso de acuerdo a una cualquiera de las reivindicaciones 1 a 17 la amina en la etapa c tiene la configuración (S)



19. Un proceso de acuerdo a una cualquiera de las reivindicaciones 1 a 18 en donde el solvente en la etapa e es t-butilmetil éter.
20. Un proceso de acuerdo a una cualquiera de las reivindicaciones 1 a 19 en donde en la etapa h el tratar con agua es mediante una atmósfera de agua saturada.
21. Un proceso para la preparación de una sal de ácido 6-[fenilo(sustituido)]-tiazolopirimidina dicarboxílico y como una sal hidratada de la fórmula (II)



(II)

En donde:

R^1 es CF_3 o C_2F_5 ;

R^2 es H o alquilo C_1-C_3 ;

n es un entero de 2, 3 o 4;

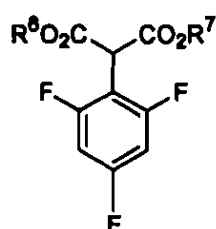
X es Cl;

R^3 y R^4 son cada uno independientemente H o alquilo C_1-C_2 ;

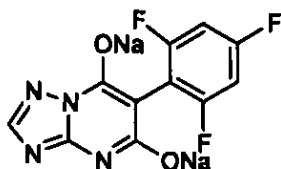
En donde la línea punteada es un enlace opcional,

Cuyo proceso comprende:

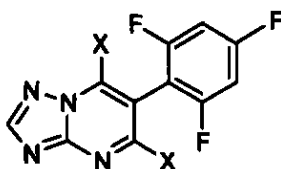
a. hacer reaccionar éster de ácido malónico de la fórmula



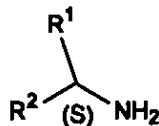
Donde R^6 y R^7 son independientemente alquilo C_1-C_3 con 3-amino-1,2,4-triazol, en una proporción en mol de aproximadamente 1:1 en la presencia de tributilamina y calentando a aproximadamente 150° C durante aproximadamente 1 a 6 h, enfriando a aproximadamente 130° C, diluyendo con tolueno, enfriando a aproximadamente 20° C a aproximadamente 30° C, y agregando al menos dos equivalentes de hidróxido de sodio acuoso y aislando la sal disodio de la fórmula



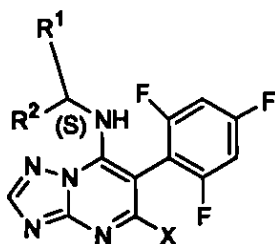
- b. Halogenar la sal de disodio con reactivo POX_3 donde X es Cl al calentar a reflujo durante aproximadamente 16 h para obtener el producto halogenado de la fórmula



- c. hacer reaccionar el producto halogenado con una amina

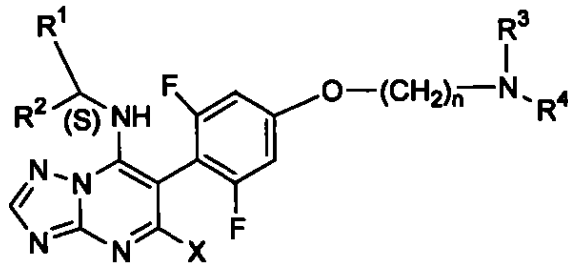


- En un solvente aprótico a aproximadamente 20°C a aproximadamente 30°C durante aproximadamente 24-48 horas para obtener un producto amina de la fórmula

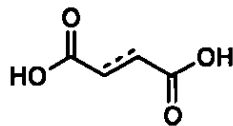


- d. Hacer reaccionar un hidruro de metal alcalino con una amino alcohol $\text{HO}-(\text{CH}_2)_n-\text{NR}^3\text{R}^4$ durante 30 minutos en tetrahidrofurano a temperatura ambiente, agregando el

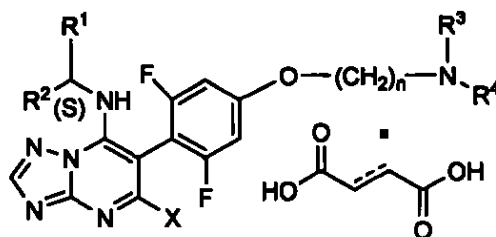
producto amina y calentando a aproximadamente 55-60° C durante aproximadamente 2-20 horas para obtener el producto 6-[fenilo(sustituido)]-tiazolopirimidina.



e. hacer reaccionar el producto 6-[fenilo(sustituido)]-tiazolopirimidina en agua con un ácido carboxílico de la fórmula.

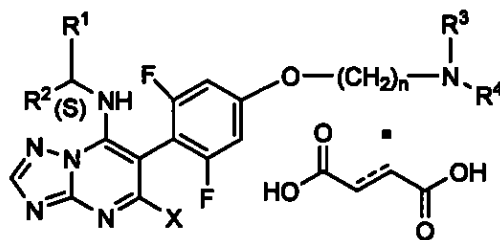


En donde la línea punteada es un enlace opcional al agregar t-butilmetil éter para obtener la sal de ácido 6-[fenilo(sustituido)]-tiazolopirimidina dicarboxílico



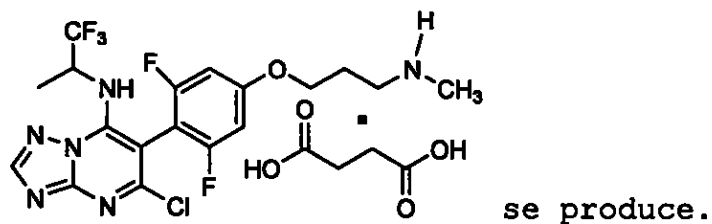
f. cristalizar la sal de ácido 6-[fenilo(sustituido)]-tiazolopirimidina dicarboxílico de agua y recolectar la sal de ácido 6-[fenilo(sustituido)]-tiazolopirimidina dicarboxílico;

- g. formar la sal de ácido 6-[fenilo(sustituido)]-tiazolopirimidina dicarboxílico anhidra al secar la sal de ácido 6-[fenilo(sustituido)]-tiazolopirimidina; y
- h. tratar la sal de ácido 6-[fenilo(sustituido)]-tiazolopirimidina dicarboxílico con agua en una atmosfera de agua saturada para obtener una sal de ácido 6-[fenilo(sustituido)]-tiazolopirimidina dicarboxílico como una sal hidratada de fórmula (II)

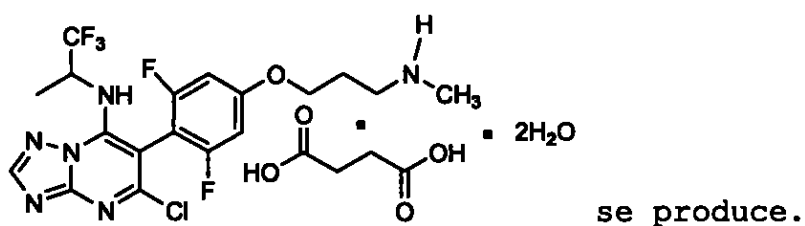


(II)

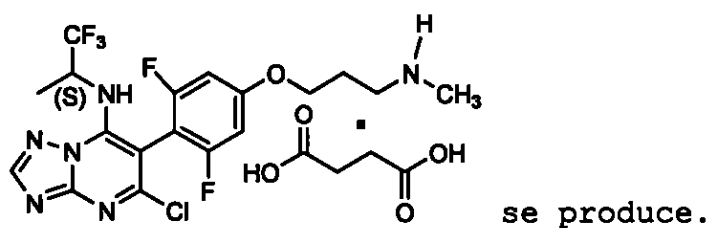
22. Un proceso de acuerdo a una cualquiera de las reivindicaciones 1 a 20 en donde



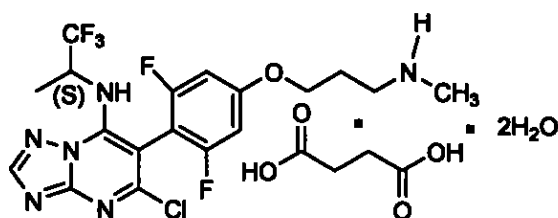
23. Un proceso de acuerdo a una cualquiera de las reivindicaciones 1 a 20 donde



24. Un proceso de acuerdo a la reivindicación 21 en donde



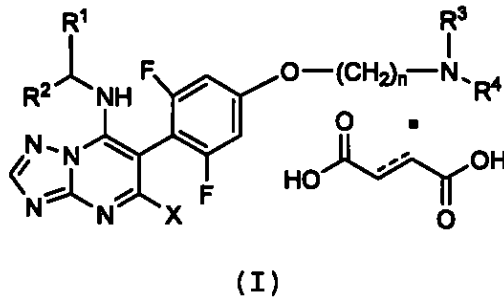
25. Un proceso de acuerdo a la reivindicación 21 en donde



26. Un proceso de acuerdo a una cualquiera de las reivindicaciones 1 a 22 en donde la proporción en mol del producto halogenado amina en la etapa C es aproximadamente 1:2 a 1:3

RESUMEN

La presente invención suministra un proceso para la preparación de sal de ácido 6-[fenilo(sustituido)]-tiazolopirimidina dicarboxílico y como sal hidratada que tiene la formula estructural (I)



En donde:

R^1 es CF_3 o C_2F_5 ;

R^2 es H o alquilo C_1-C_3 ;

n es un entero de 2, 3 o 4;

X es Cl;

R^3 y R^4 son cada uno independientemente H o alquilo C_1-C_3 ; o

R^3 y R^4 cuando se toman opcionalmente juntos con el átomo de nitrógeno al cual cada uno esta unido forman un anillo de heterocíclicos saturado de 4 a 6 miembros que tiene 1-2 átomos de nitrógeno y 0-1 átomos de oxígeno o 0-2 átomos de azufre y opcionalmente sustituido con R^5 ;

R^5 es alquilo C_1-C_3 ;

En donde la línea punteada es un enlace opcional.

PATENT COOPERATION TREATY

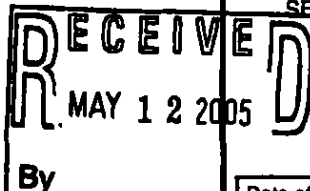
P

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To
 WYETH
 Patent Law Department
 Attn. Calnan, William H.
 Five Giralda Farms
 Madison, New Jersey 07940
 UNITED STATES OF AMERICA

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



(PCT Rule 44.1)

Applicant's or agent's file reference
 AM101480

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
 PCT/US2004/040854

International filing date
 (day/month/year) 07/12/2004

Applicant
 WYETH

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

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46)

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

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
 1211 Geneva 20, Switzerland, Facsimile No. (41-22) 740 14.35

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

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

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

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made

4. Reminders

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

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

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

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

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

Name and mailing address of the International Searching Authority

 European Patent Office, P B 5818 Patentlaan 2
 NL-2280 HV Rijswijk
 Tel (+31-70) 340-2040, Tx 31 651 epo nl,
 Fax (+31-70) 340-3018

Authorized officer

Stefan Brel

DOCKETED

DUE DATE

STAT DATE

BY

7/6/05
 105/16/05

CC: PEARL

CC: TAPLOW

NOTES TO FORM PCT/ISA/220

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

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

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

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

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

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

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

When?

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

Where not to file the amendments?

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

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

How?

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

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

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

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

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

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

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

NOTES TO FORM PCT/ISA/220 (continued)

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

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

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

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

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

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

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

It must be in the language in which the international application is to be published.

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

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

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

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

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

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

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

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

PATENT COOPERATION TREAT

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference AM101480	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below	
International application No PCT/US2004/040854	International filing date (day/month/year) 07/12/2004	(Earliest) Priority Date (day/month/year) 08/12/2003
Applicant WYETH		

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

This International Search Report consists of a total of 4 sheets.

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

1 Basis of the report

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

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

b ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2 ☐ Certain claims were found unsearchable (See Box II).

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

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

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

5 With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6 With regard to the drawings,

a the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant

☐ as selected by this Authority, because the applicant failed to suggest a figure

☐ as selected by this Authority, because this figure better characterizes the invention

b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/040854A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	WO 99/48893 A (AMERICAN CYANAMID COMPANY) 30 September 1999 (1999-09-30) the whole document	1-26
A	EP 0 770 615 A (AMERICAN CYANAMID COMPANY; BASF AKTIENGESELLSCHAFT) 2 May 1997 (1997-05-02) the whole document	1-26
A	US 6 117 876 A (PEES ET AL) 12 September 2000 (2000-09-12) the whole document	1-26

☐ Further documents are listed in the continuation of box C☒ Patent family members are listed in annex

* Special categories of cited documents

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

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

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

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

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

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

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

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

S document member of the same patent family

Date of the actual completion of the international search

26 April 2005

Date of mailing of the international search report

06/05/2005

Name and mailing address of the ISA

European Patent Office, P B 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Stroeter, T

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/040854

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9948893	A	30-09-1999	US 5981534 A	09-11-1999
			AT 239727 T	15-05-2003
			AT 228133 T	15-12-2002
			AU 752669 B2	26-09-2002
			AU 3098599 A	18-10-1999
			AU 735730 B2	12-07-2001
			AU 6867198 A	11-11-1998
			BG 64197 B1	30-04-2004
			BG 103805 A	30-06-2000
			BR 9808531 A	23-05-2000
			BR 9909009 A	28-11-2000
			CA 2287470 A1	22-10-1998
			CA 2324154 A1	30-09-1999
			CN 1302299 A , C	04-07-2001
			CN 1528762 A	15-09-2004
			CZ 20003472 A3	16-01-2002
			CZ 292092 B6	16-07-2003
			DE 69814375 D1	12-06-2003
			DE 69814375 T2	24-12-2003
			DE 69903988 D1	02-01-2003
			DE 69903988 T2	27-03-2003
			DK 975635 T3	02-06-2003
			DK 945453 T3	16-12-2002
			EA 2906 B1	31-10-2002
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

CT/US2004/040854

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EP 0770615	A	PT 770615 T	31-10-2003
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)Applicant's or agent's file reference
see form PCT/ISA/220FOR FURTHER ACTION
See paragraph 2 belowInternational application No
PCT/US2004/040854International filing date (day/month/year)
07 12.2004Priority date (day/month/year)
08 12.2003International Patent Classification (IPC) or both national classification and IPC
C07D487/04Applicant
WYETH

1 This opinion contains indications relating to the following items

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

2 FURTHER ACTION

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

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

For further options, see Form PCT/ISA/220

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

Name and mailing address of the ISA



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Authorized Officer

Stroeter, T

Telephone No +49 89 2399-8088



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No
PCT/US2004/040854**Box No. I Basis of the opinion**

- 1 With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23 1(b))
- 2 With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of
 - a type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b format of material
 - ☐ in written format
 - ☐ in computer readable form
 - c time of filing/furnishing
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form
 - ☐ furnished subsequently to this Authority for the purposes of search.
- 3 ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
- 4 Additional comments

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No
PCT/US2004/040854**Box No. V Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement****1 Statement**

Novelty (N)	Yes	Claims	1-26
	No	Claims	
Inventive step (IS)	Yes	Claims	1-26
	No	Claims	
Industrial applicability (IA)	Yes	Claims	1-26
	No	Claims	

2 Citations and explanations**see separate sheet**

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/040854

Re Item V.

- 1 Reference is made to the following documents:
D1 : WO 99/48893 A (AMERICAN CYANAMID COMPANY) 30 September 1999
(1999-09-30)
D2 : EP 0 770 615 A (AMERICAN CYANAMID COMPANY; BASF
AKTIENGESELLSCHAFT) 2 May 1997 (1997-05-02)
D3 : US 6 117 876 A (PEES ET AL) 12 September 2000 (2000-09-12)
- 2 The present application is directed to a process for the preparation of certain 6-(substituted phenyl)triazolopyrimidine dicarboxylic acid salts which are tubulin inhibitors and are useful in the treatment of cancer.
- 3 Documents D1-D3, which are considered to represent the most relevant state of the art, disclose processes for the preparation of 6-(substituted phenyl)triazolopyrimidine corresponding to present steps a - c but lack the formation of the present products wherein the characterizing side group O-Alkylene-NR³R⁴ is attached at the phenyl ring in the last step d. Since the introduction of such a group was neither described nor suggested in the related prior art, the presently claimed process(es) is/are both novel and inventive (Article 33(2) and (3) PCT).

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL
TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION (✓) MODELO DE UTILIDAD ()	()	()
-Indicación de  e se solicita la concesión de una patente.	(✓)	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	(✓)	()
-Descripción de la invención.	(✓)	()
-Dibujos de ser estos pertinentes.	(✓)	()
-Comprobante de Pago de las tasas establecidas.	(✓)	()
COMPLETA (✓) INCOMPLETA ()	()	()
DISEÑO INDUSTRIAL ()		
-Indicación de que se solicita el registro de Diseño Industrial.	()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
-Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
-Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA () INCOMPLETA ()	()	()
ESQUEMA DE TRAZADO ()		
-Indicación de que se solicita el registro de Diseño Industrial.	()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
-Representación gráfica del Esquema Trazado.	()	()
-Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA () INCOMPLETA ()	()	()

Firma Responsable:

Fecha:


Junio 8, 2006