



No. 13-115442-00000-0000

Fecha: 2013-05-08 16:44:31 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 4



Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCION

TITULO: SAL(ES) DE DIMETIL-AMIDA DEL ÁCIDO 7-CICLOPENTIL-2-(5-PIPERAZIN-1-IL-PIRIDIN-2-IL-AMINO)-7H-PIRROLO-[2,3-D]-PIRIMIDIN-6-CARBOXÍLICO Y PROCESOS PARA SU ELABORACIÓN

SOLICITANTE: NOVARTIS AG Y ASTEX THERAPEUTICS LTD.

DIRECCIÓN: Lichtstrasse 35, CH-4056 Basel y 436 Cambridge Science Park, Milton Road, Cambridge Cambridgeshire CB4, 0QA.

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 08 de Mayo de 2012

P2013/000067



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PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL

P2013/000067

SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☒

Capítulo I.

☐

Capítulo II.

2

SOLICITANTE
(71)Nombre: NOVARTIS AG Y ASTEX
THERAPEUTICS LTD.Dirección: Lichtstrasse 35, CH-4056 Basel y
436 Cambridge Science Park, Milton Road,
Cambridge Cambridgeshire CB4, 0QA.Nacionalidad o Domicilio: Suiza y Gran
BretañaLugar de Constitución: Suiza y Gran
BretañaTeléfono: _____ Fax: _____
E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número _____

REPRESENTANTE
O APODERADONombre: CARLOS R. OLARTEDirección: Carrera 5 No 34-03 Bogotá D.C.Teléfono: 601-7700 Fax: 601-7799E-mail: office@olartemoure.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número 79782747Bta
TP 74.295INVENTOR (ES)
(72)Nombre: VER PAGINA ADJUNTADirección: VER PAGINA ADJUNTANacionalidad o Domicilio: VER PAGINA ADJUNTA

5

PCT (86)

Solicitud Internacional No. PCT/US2011/059890Fecha Noviembre 09, 2011Publicación Internacional No. WO 2012/064805 A1Fecha Mayo 18, 2012

6

Título (54) SAL(ES) DE DIMETIL-AMIDA DEL ÁCIDO 7-CICLOPENTIL-2-(5-
PIPERAZIN-1-IL-PIRIDIN-2-IL-AMINO)-7H-PIRROLO-[2,3-D]-PIRIMIDIN-6-
CARBOXÍLICO Y PROCESOS PARA SU ELABORACIÓN

Clasificación Internacional (51) C07D 401/12; A61K 31/519; A61P 35/00

Prioridad

SI ☒ NO ☐

(33) País de Origen

US

(32) Fecha

Noviembre 10, 2010

(31) Número de
Solicitud

61/412.064



ANEXOS



Comprobante de pago de la tasa de presentación de la solicitud.



Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.



Poderes, si fuere el caso. Adjunto copia simple.



Documento de cesión del inventor al solicitante o a su causante.



Declaraciones. Declaración bajo la regla 4.17 (ii) del PCT.



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.



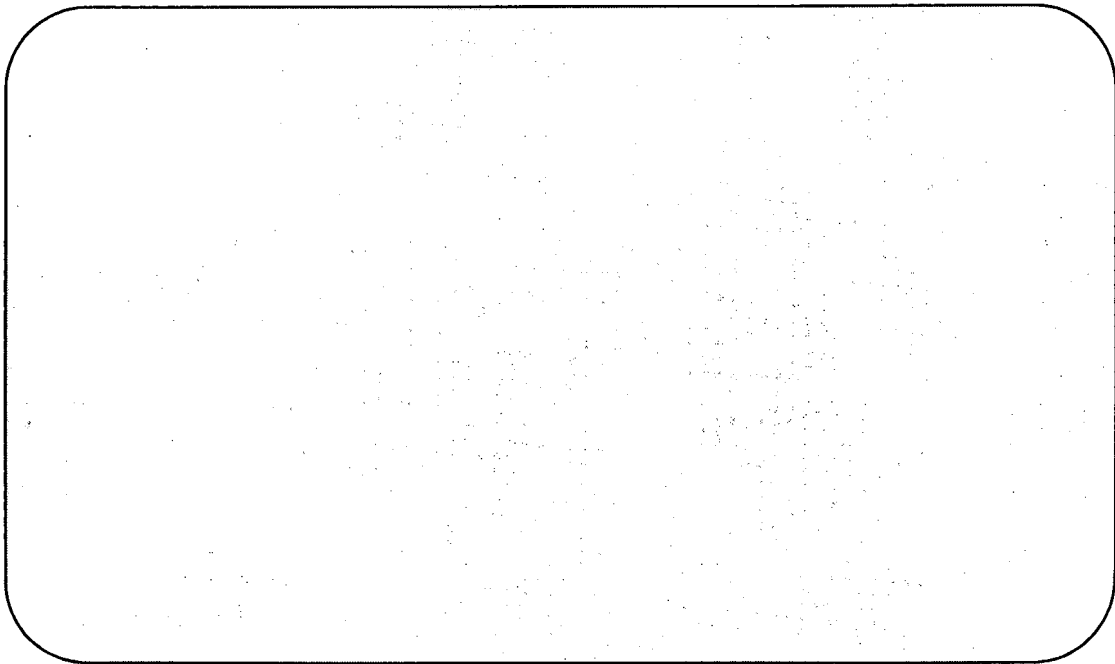
De ser el caso, modificaciones efectuadas a la solicitud internacional.



Otros. Búsqueda Internacional



FIGURA CARACTERÍSTICA:



Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

3

LISTA DE INVENTORES

PCT/US2011/059890

John Vincent CALIENNI

Novartis Pharmaceuticals Corporation,
One Health Plaza, East Hanover,
New Jersey 07936
Estados Unidos de América
Nacionalidad: Estadounidense

Guang-Pei CHEN

33 Preston Drive
Livingston, Nueva Jersey 07039
Estados Unidos de América
Nacionalidad: Estadounidense

Baoqing GONG

Novartis Pharmaceuticals Corporation,
One Health Plaza, East Hanover,
New Jersey 07936
Estados Unidos de América
Nacionalidad: Estadounidense

Prasad Koteswara KAPA

Novartis Pharmaceuticals Corporation,
One Health Plaza, East Hanover,
New Jersey 07936
Estados Unidos de América
Nacionalidad: Estadounidense

Vishal SAXENA

2001 Falls Boulevard,
Apt. 124, Quincy,
Massachusetts 02169
Estados Unidos de América
Nacionalidad: Indú

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

 Industria y Comercio SUPERINTENDENCIA	RECIBO DE CAJA	No. 13 - 0032237
		Bogotá D.C., Abril 08 de 2013 - 11:50:13

RECIBIDO DE : OLARTE MOURE & ASOCIADOS					NI 830.122.870
*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	181981796	05/04/2013	9.515.000.00

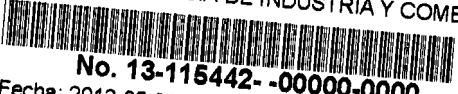
*** Conceptos Pagados ***			
CANT. RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN	500.000.00	500.000.00
			\$500.000.00

SON: **QUINIENTOS MIL PESOS MONEDA CORRIENTE**

Responsable: 

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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PATENTE DE INVENCION ☐

MODELO DE

☐	Indicación que se solicita una patente.
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Descripción de la invención
☐	Dibujos de ser estos pertinentes
☐	Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)
Completa ☐	Incompleta ☐

PATENTE DE INVENCION PCT ☒ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

1 ☒	Indicación que se solicita una PCT
2 ☒	Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
3 ☒	Dibujos de ser estos pertinentes
4 ☒	Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)
Completa ☒	Incompleta ☐

DISEÑO INDUSTRIAL ☐

(Art. 119 Decisión 486/00)

☐	Indicación que se solicita Diseño industrial
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
☐	Comprobante de pago de las tasas establecidas
Completa ☐	Incompleta ☐

ESQUEMA DE TRAZADO ☐

(Art. 92 Decisión 486/00)

☐	Indicación que se solicita un esquema de trazado
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica de un esquema de trazado
☐	Comprobante de pago de las tasas establecidas
Completa ☐	Incompleta ☐

Nota del traductor:

El documento adjunto de poder de Novartis AG a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva los siguientes datos en inglés.

CERTIFICACIÓN NOTARIAL

1. En esta fecha, día 30 de Agosto de 2006, yo, el suscrito Notario Público certifico por medio del presente la autenticidad de las firmas del señor Arthur Canonica, ciudadano de Corticiasca, Suiza, residente en Wisen/SO, Suiza, y del Sr. Pascal Traub, ciudadano de Riehen, Suiza, residente en Basilea, Suiza, ambos personas mayores de edad y con dirección comercial en Lichstrasse 35, 4056, Basilea, Suiza. La autenticidad de la firmas fue establecida por medio de la comparación.
2. Además, yo, el Notario Público, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG.
3. Además, yo, el Notario Público certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, está debidamente constituida, está actualmente vigente y que los propósitos para los cuales se otorgó el Documento de Poder están dentro del alcance de sus propósitos corporativos.



4. Además, yo, el Notario Público, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el documento de Poder y que por este instrumento, su representación es legal.

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibición de los siguientes documentos auténticos:

- Documento de Poder de Novartis AG fechado el 19 de junio de 2006 y
- Extracto del Registro de Comercio del Cantón de la ciudad de Basilea para Novartis AG, en Basilea, fechado el 25 de enero de 2006.

Basilea, Suiza, este día 30 de Agosto de 2006.

(Firmado) Dr. Matthias Staehelin, Notario Público del Cantón de la ciudad de Basilea, Suiza.

Mi licencia vence el 11 de Marzo de 2009.

Hay una Apostilla de Suiza, firmada por Heidi Fischer, bajo el No. 8049/13584.



Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Novartis"

Fecha: 12 de Septiembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

Teléfono: (57-1) 2182308, (57-1) 6232925.

E-mail: treseser1@yahoo.com. No. 8346



Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

Power of Attorney

The undersigned,

domiciled in

NOVARTIS AG

Lichtstrasse 35, CH-4056 Basel / Switzerland

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

domiciliado en

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

Date/Fecha: June 27, 2006

City/Country/Ciudad,País: Basel, Switzerland


Arthur Canonica


Pascal Traub

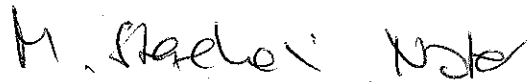
Attestation

- 1 On this date, the 30th (thirtieth) day of August 2006 (two thousand and six), I, the undersigned Notary Public certify herewith the authenticity of the signatures of **Mr. Arthur Canonica**, citizen of Corticiasca, Switzerland, residing in Wisen/SO, Switzerland and of **Mr. Pascal Traub**, citizen of Riehen, Switzerland, residing in Basel, Switzerland, both of legal age and with business address at, Lichtstrasse 35, 4056 Basel, Switzerland. The authenticity of the signatures was established by means of comparison.
- 2 Further, I, the Notary Public certify herewith that the foregoing persons have executed the foregoing document as proxy holders for Novartis AG.
- 3 Further, I, the Notary Public certify herewith that Novartis AG, having its principal place of business located in Basel / Switzerland, is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.
- 4 Further, I, the Notary Public certify herewith that the foregoing persons have the authority to execute the Power of Attorney and that for this instrument their representation is legal.

The foundation for my certifications contained in points 2 (two), 3 (three) and 4 (four) was the exhibition of the following authentic documents:

- Power of Attorney by Novartis AG dated June 19 (nineteen), 2006 (two thousand and six); and
- Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty-five), 2006 (two thousand and six).

BASEL, Switzerland, this 30th (thirtieth) day of August 2006 (two thousand and six)



Dr. Matthias Staehelin, Notary Public
in the Canton of Basel-City, Switzerland

My license expires on March 11 (eleven),
2009 (two thousand and nine).

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)

This official document

2. is signed by *P. in*

3. in his/her function as *St. Stettelin*

4. and certified by the seal of the *St. Stettelin*

Certified 20. Aug. 2006

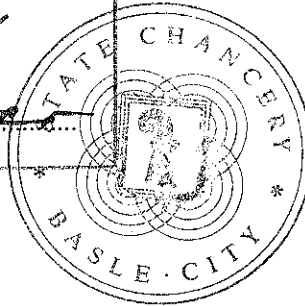
5. in Basel (Bâle) 6. on

7. by the State Chancery of the Canton of Basel-Stadt

8. no. *2009/18584*

9. Seal / stamp: 10. Signature: *Fischer*

Heidi Fischer





2729



ESCRITURA PÚBLICA NÚMERO:

DOS MIL SETECIENTOS VEINTINUEVE (2729) - - - - -

FECHA DE OTORGAMIENTO:

CUATRO (04) DE ABRIL DE DOS MIL ONCE (2011) - - - - -

NOTARIA TREINTA Y OCHO (38) DEL CÍRCULO DE BOGOTÁ D.C. -----

SUPERINTENDENCIA DE NOTARIADO Y REGISTRO.-----

CÓDIGO NOTARIAL 1100100038. -----

FORMULARIO DE CALIFICACIÓN. -----

CLASE DE ACTO: PROTOCOLIZACIÓN DE DOCUMENTOS. -----

PERSONAS QUE INTERVIENEN: CARLOS REINALDO OLARTE, identificado con la cédula de ciudadanía número 79.782.747 expedida en Bogotá.-----

En la ciudad de Bogotá, Distrito Capital, Departamento de Cundinamarca, República de Colombia, a los CUATRO ---- (04--) días del mes de ABRIL - - -

de dos mil once (2011), ante mí RODOLFO REY BERMUDEZ - - - - -

NOTARIO(A) TREINTA Y OCHO (38_E) DEL CÍRCULO DE BOGOTÁ D.C.-----

Compareció: **CARLOS REINALDO OLARTE,** mayor de edad, domiciliado y residente en la ciudad de Bogotá D.C., identificado con la cédula de ciudadanía número 79.782.747 expedida en Bogotá, de estado civil casado con sociedad conyugal vigente, quien obra en nombre propio y manifestó:-----

PRIMERO.- Presenta para su Protocolización los siguientes documentos: -----

1. Cuatro (04) folios útiles, en los que consta El **Poder General** otorgado por ASTEX THERAPEUTICS LTD. al señor CARLOS R. OLARTE, de fecha 22 de Febrero de 2011 ante el Notario Público en Reino Unido de Gran Bretaña e Irlanda del Norte, texto en inglés y español y su respectiva Apostilla.-----

SEGUNDO.- Que de conformidad con lo expuesto y atendiendo a las prescripciones del artículo 56, 57 y 58 del Decreto 960 de 1970, los documentos mencionados, contenidos en cuatro (04) folios útiles, quedan legalmente protocolizados ante el Notario Treinta y Ocho (38) del Círculo Bogotá, de manera que desde ahora quedan bajo su custodia y guarda para que surtan los efectos legales a que haya lugar y los interesados puedan consultarlos y obtener las copias que de el solicite. -----



HASTA AQUÍ LA MINUTA

SE ADVIRTIÓ al (a los) otorgante (s) de esta escritura de la **obligación que tiene (n) de leer la totalidad de su texto**, a fin de verificar la exactitud de todos los datos en ella consignados con el fin de aclarar, modificar o corregir lo que le(s) pareciere; la firma de la misma demuestra su aprobación total del texto.-----

Se advierte igualmente la necesidad de diligenciar los espacios en blanco correspondientes a la información personal y de trabajo consignados en el espacio destinado para la firma de los suscriptores del instrumento publico, con el objeto de confrontar la información solicitada con el contenido de la escritura previo a la autorización de la misma. -----

En consecuencia, la notaria no asume ninguna responsabilidad por error o inexactitudes establecidas con posterioridad a la firma del (los) otorgante (s) y del notario. -----

En tal caso, de la existencia de estos, deben ser corregidos mediante el otorgamiento de una nueva escritura, suscrita por el (los) que intervino (eron) en la inicial y sufragada por el (ellos) mismo (s). (Articulo 35 decreto ley 960 de 1.970).-----

ADVERTENCIA PARA TODOS LOS COMPARECIENTES QUE EXTIENDAN Y OTORGUEN INSTRUMENTOS, SEGÚN ART. 34 C.N., LEY 190 DE 1995, LEY 333 DE 1996 Y LEY 365 DE 1997. Los comparecientes bajo la gravedad del juramento manifiestan clara y expresamente que todos los dineros, bienes muebles e inmuebles contenidos en este instrumento fueron adquiridos por medios y actividades lícitas. Así como el dinero con el que se efectúa el pago de los gastos notariales.-----

OTORGAMIENTO Y AUTORIZACIÓN. Leído el presente instrumento por el otorgante y advertido de la formalidad de Ley, estuvo de acuerdo con él lo aceptó en la forma como está redactado y en testimonio de que le da su asentimiento y aprobación lo firma por ante mí y conmigo el Notario que de todo lo expuesto doy fe lo autorizo.-----

CONSTANCIA: El presente instrumento se extiende en la siguiente hoja de papel Notarial No. 7 700094 654716/ 654723/ - - - - -

- - - - -

7 700094 654723

Pág. No 3



FOLIO ANTERIOR

7 700094 654716 - - - - -

ESCRITURA PÚBLICA NÚMERO:

DOS MIL SETECIENTOS VEINTINUEVE (2729) - - - - -

FECHA DE OTORGAMIENTO:

CUATRO (04) DE ABRIL DE DOS MIL ONCE (2011) - - - - -

NOTARIA TREINTA Y OCHO (38) DEL CÍRCULO DE BOGOTÁ D.C. - - - - -

RETENCIÓN EN LA FUENTE. ARTÍCULO 20 Y 64 LEY 0075 DE 1986.\$ EXENTO - - - - -

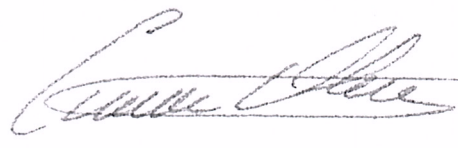
DERECHOS NOTARIALES.....\$ 44.000 - - - - -

SUPERINTENDENCIA.....\$3.700.00. - - - - -

FONDO NACIONAL DEL NOTARIADO.....\$3.700.00. - - - - -

IVA\$ 14.080 - - - - -

DECRETO 1681 DE SEPTIEMBRE 16 DE 1996 Y RESOLUCIÓN 11621 DE
DICIEMBRE 22 DE 2010 Y MODIFICADA POR LA RESOLUCIÓN 11903 DE
DICIEMBRE 30 DE 2010. - - - - -



CARLOS REINALDO OLARTE

C.C. 79782.747

DIRECCIÓN RESIDENCIA: DIAGONAL 34 N° 5-28.

DIRECCIÓN OFICINA: DIAGONAL 34 N° 5-28.

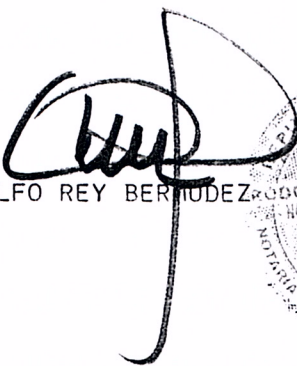
TELÉFONO RESIDENCIA: 601-7700

TELÉFONO OFICINA: 601-7700

CELULAR: 315 790 1625.

ESTADO CIVIL: CASADO.

EL NOTARIO TREINTA Y OCHO (38)
DEL CIRCULO DE BOGOTA, D.C.


RODOLFO REY BERMUDEZ
NOTARIO TREINTA Y OCHO (38)
CIRCULO DE BOGOTA, D.C.

Y. ZOLAQUE

Z. HDEZ

ROBERTO M. OLARTE GARCIA
Traductor e Intérprete Oficial
Resolución No. 0041
Minijusticia 1996



Este documento público es una traducción al español de un documento en idioma inglés
presentado ante mí el 28 de marzo de 2011.

ROBERTO M. OLARTE GARCÍA
Traductor e Intérprete Oficial
Ministerio de Justicia
Licencia 0041/1996

4149

CERTIFICACIÓN NOTARIAL

Sección quinta:

El fundamente de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición del
siguiente documento auténtico:

Formulario 288a “Nombramiento de Director o Secretario” el cual nombra a Harren Jhoti
como Director de Astex Technology Limited (Número de compañía 3751674) el 18 de
mayo de 1999, compañía la cual cambió su razón social a Astex Therapeutics Limited el 27
de junio de 2005 según acta de constitución en cambio de nombre.

NOTARIO PÚBLICO (firma):

(firma: ilegible)

16/2/11

PETER C.FLETCHER

Solicitante (a mano: Notario Público)

186A Victoria Road

Cambridge CB4 3LG

Tel. 01223 566596

(sello: ilegible)

APOSTILLA
(Convención de La Haya del 5 de octubre de 1961)

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte

Este documento público

2. Ha sido firmado por **Peter C Fletcher**
3. Actuando en calidad de **Notario Público**
4. Lleva el sello de **dicho Notario Público**
5. en Londres
6. certifica el **22 de febrero de 2011**

7. por el Secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de Mancomunidad

8. Número **I788425**

9. Sello: (Oficina de la Mancomunidad y del Exterior – Londres)

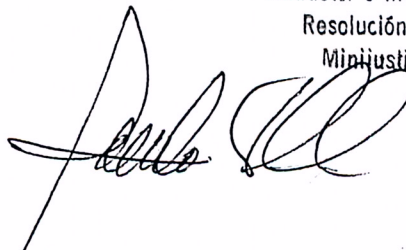
10. Firma: **G Marshall** (firma ilegible)

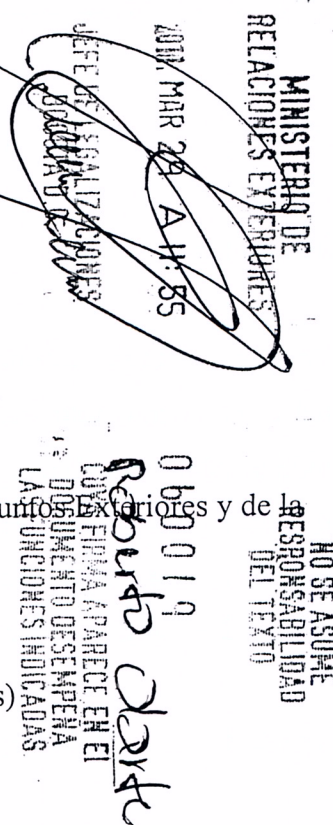
(e) Secretario de Estado

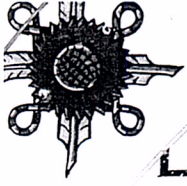
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ROBERTO M. OLARTE GARCIA
Traductor e Intérprete Oficial
Resolución No. 0041
Minjusticia 1996







OLARTE MOURE

OLARTE MOURE & ASOCIADOS LTDA.

General Power of Attorney

The undersigned,

domiciled in

436 Cambridge Science Park, Milton Road, Cambridge CB4, 0QA, Great Britain.

hereby appoint to **Carlos R. Olarte** as legal representative with authority to appoint judicial or extrajudicial agents for matters related to **Patents for Inventions and Industrial Designs** in the Republics of Argentina, Belize, Bolivia, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Paraguay, Peru, Oriental Republic of Uruguay and the Bolivarian Republic of Venezuela, in order to initiate before any authorities all the necessary actions to accomplish these purposes and to intervene in all instances, steps and procedural levels; to file and prosecute applications, receive notifications, declarations, complaints, to claim, counterclaim, answer claims and counterclaims; to make amendments; oppositions and all types of objections and writings of any nature; cancellations and administrative injunction proceedings; to pay all installments and effect all other payments prescribed by law; to receive documents and monies; act as complainants as well as defendants, before the competent judges, with full powers to request preliminary injunctions of any nature, settle, make arrangements, to submit to arbitrators, to desist from claims or procedures, to accept claims, to collect, to ratify legal proceedings subscribed before the appointment and/or presentation of this Power, substitute or delegate the legal representation and other acts prescribed by law, in short, with all such further powers as may be required; to comply with all other requirements and, to take all those measures which he may deem fit for the protection of our interests.

Signature/Firma:

Name/Nombre: Harren Jhoti, Chief Executive Officer

Date/Fecha:

16 February 2011

City, Country/Ciudad, País: CAMBRIDGE, UK

Poder General

Los suscritos,

domiciliados en

436 Cambridge Science Park, Milton Road, Cambridge CB4, 0QA, Great Britain.

nombramos por el presente a **Carlos R. Olarte** como nuestro representante legal con facultades para nombrar apoderados judiciales o extrajudiciales para asuntos de **Patentes de Invención y Diseños Industriales** en las Repúblicas de Argentina, Belice, Bolivia, Chile, Colombia, Costa Rica, Cuba, República Dominicana, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panamá, Paraguay, Perú, República Oriental del Uruguay y la República Bolivariana de Venezuela, para iniciar ante cualquier autoridad todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales; elevar y tramitar solicitudes, recibir notificaciones, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconveniones; formular enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento, allanarse a la pretensión, percibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que crea conducentes al resguardo de nuestros intereses.

Signature/Firma:

Name/Nombre:

Date/Fecha:

City, Country/Ciudad, País:



MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

Certificación Notarial

On this date,

En esta fecha,

The undersigned Notary Public certifies:

el Notario Público suscrito certifica:

1. That

1. Que

Harren Jhoti

of legal age and domiciled in

mayor de edad y domiciliado

436 Cambridge Science Park, Milton Road, Cambridge CB4, 0QA, Great Britain.
signed the foregoing document.

suscribió el documento que antecede.

2. That the grantor has executed the foregoing document as **Chief Executive Officer** of **ASTEX THERAPEUTICS LTD.**

2. Que el otorgante ha suscrito el referido documento en su carácter de de

3. That **ASTEX THERAPEUTICS LTD.** having its principal place of business located in **436 Cambridge Science Park, Milton Road, Cambridge CB4, 0QA, Great Britain.** is duly incorporated, is currently in existence, and that the purposes for which the General Power is granted are within the scope of its corporate purposes.

4. Que con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

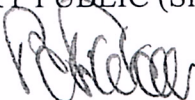
4. That the grantor has the authority to execute the General Power and that his/her representation is legal.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):
Form 288a ‘Appointment of Director or secretary’ which appoints Harren Jhoti as Director of Astex Technology Limited (Company Number 3751674) on 18 May 1999, which Company changed its name to Astex Therapeutics Limited on 27 June 2005 as evidenced by the Certificate of Incorporation on Change of Name

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature):

 16/2/11
PETER C. FLETCHER
Solicitor & Notary Public
186A Victoria Road
Cambridge CB4 3LG
Tel: 01223 566596



APOSTILLE

(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord
This public document / Le présent acte public
2. Has been signed by **Peter C Fletcher**
a été signé par
3. Acting in the capacity of **Notary Public**
agissant en qualité de
4. Bears the seal/stamp of **The Said Notary Public**
est revêtu du sceau/timbre de
5. at London/à Londres
6. Certified/Attesté
the/le **22 February 2011**
7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.
8. Number/sous No **I788425**
9. Stamp:
timbre:
10. Signature: **G Marshall**



For the Secretary of State / Pour le Secrétaire d'Etat

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PRIMERA

(1) COPIA (FOTOCOPIA) DE LA ESCRITURA

No. 2729 DE FECHA CUATRO (4) DEL MES DE ABRIL

DE DOS MIL ONCE (2011) TOMADA DE SU ORIGINAL CONFORME

AL ART. 41 DEL DECRETO 2148 DE 1983, QUE SE EXPIDE EN BOGOTÁ, D.C.,

A CUATRO (4) DEL MES DE ABRIL

DE DOS MIL ONCE (2011), EN SEIS (6) FOLIOS

UTILES CON DESTINO A: EL INTERESADO

RODOLFO REY BERMUDEZ

NOTARIO TREINTA Y OCHO (38E)



VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application NOVARTIS AG is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(i) v)		an assignment from CALIENNI, John Vincent to NOVARTIS PHARMACEUTICALS CORPORATION, dated 20 October 2011 (20.10.2011)
VIII-2-1(i) v)		an assignment from CHEN, Guang-Pei to NOVARTIS PHARMACEUTICALS CORPORATION, dated 22 October 2011 (22.10.2011)
VIII-2-1(i) v)		an assignment from GONG, Baoqing to NOVARTIS PHARMACEUTICALS CORPORATION, dated 20 October 2011 (20.10.2011)
VIII-2-1(i) v)		an assignment from KAPA, Prasad Koteswara to NOVARTIS PHARMACEUTICALS CORPORATION, dated 20 October 2011 (20.10.2011)

VIII-2-2	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application NOVARTIS AG is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-2(i v)		an assignment from NOVARTIS PHARMACEUTICALS CORPORATION to NOVARTIS AG, dated 07 November 2011 (07.11.2011)

VIII-2-3	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application NOVARTIS AG is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-3(i v)		an assignment from SAXENA, Vishal to NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, INC., dated 31 October 2011 (31.10.2011)

VIII-2-4	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application NOVARTIS AG is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-4(i v)		an assignment from NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, INC. to NOVARTIS AG, dated 03 November 2011 (03.11.2011)

VIII-2-5	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application ASTEX THERAPEUTICS LTD is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-5(i v)		an assignment from NOVARTIS AG to ASTEX THERAPEUTICS LTD, dated 08 November 2011 (08.11.2011)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 May 2012 (18.05.2012)

(10) International Publication Number
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(72) Inventors; and

(75) Inventors/Applicants (for US only): **CALIENNI, John Vincent** [US/US]; Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, New Jersey 07936 (US). **CHEN, Guang-Pei** [US/US]; 33 Preston Drive, Livingston, New Jersey 07039 (US). **GONG, Baoqing** [US/US]; Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, New Jersey 07936 (US). **KAPA, Prasad Koteswara** [US/US]; Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936 (US). **SAXENA, Vishal** [IN/US]; 2001 Falls Boulevard, Apt. 124, Quincy, Massachusetts 02169 (US).

(74) Agent: **RUECK, Sandra S.**; Novartis Pharmaceuticals Corporation, Patent Department, One Health Plaza, East Hanover NJ, New Jersey 07936 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

— with international search report (Art. 21(3))
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: SALT(S) OF 7-CYCLOPENTYL-2-(5-PIPERAZIN-1-YL-PYRIDIN-2-YLAMINO)-7H-PYRROLO[2,3-D]PYRIMIDINE-6-CARBOXYLIC ACID DIMETHYLAMIDE AND PROCESSES OF MAKING THEREOF

(57) Abstract: This invention relates to (1) process of making 7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide and salts thereof; (2) novel salt(s) of 7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide; (3) pharmaceutical compositions comprising the same; and (4) methods of treatment using the same.



WO 2012/064805 A1

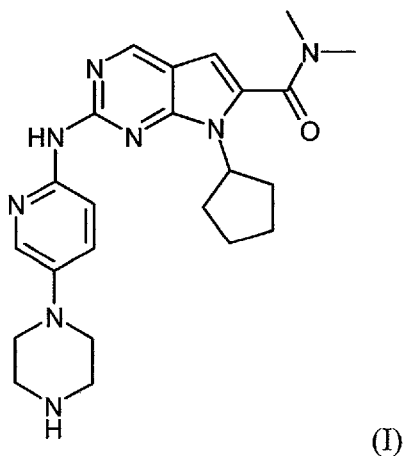
SALT(S) OF 7-CYCLOPENTYL-2-(5-PIPERAZIN-1-YL-PYRIDIN-2-YLAMINO)-7H-PYRROLO[2,3-D]PYRIMIDINE-6-CARBOXYLIC ACID DIMETHYLAMIDE AND PROCESSES OF MAKING THEREOF

Field of the Invention

This invention relates to (1) process of making 7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide and salt(s) thereof; (2) novel salt(s) of 7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide; (3) pharmaceutical compositions comprising the same; and (4) methods of treatment using the same.

Related Background Art

The compound 7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide of Formula (I)



and its synthesis is specifically described in WO 2010/020675 A1, Example 74.

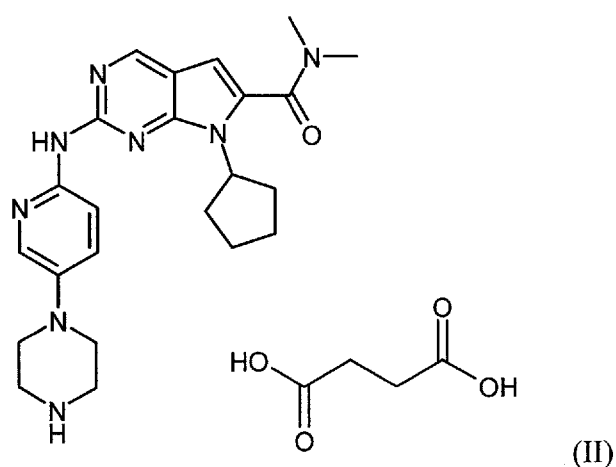
WO2010/020675 discloses that compound of Formula (I) has valuable pharmacological properties and can be used, for example, (1) as inhibitors of cyclin dependent kinases, (in particular, cyclin dependent kinases selected from CDK1, CDK2, CDK3, CDK4, CDK5, CDK6 and CDK9); and (2) as modulators and/or inhibitors of glycogen synthase kinase-3 (GSK-3).

WO2010/020675 does not disclose or suggest the succinate salt of 7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide.

Summary of the Invention

The present invention is directed to succinate salt of 7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide.

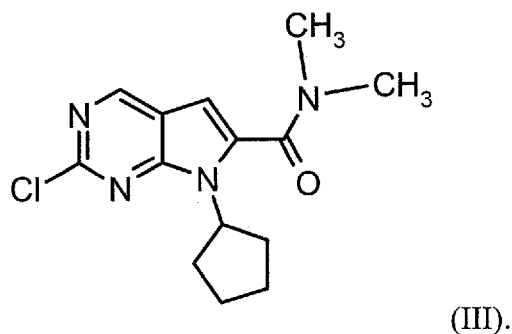
The succinate salt is described by Formula (II):



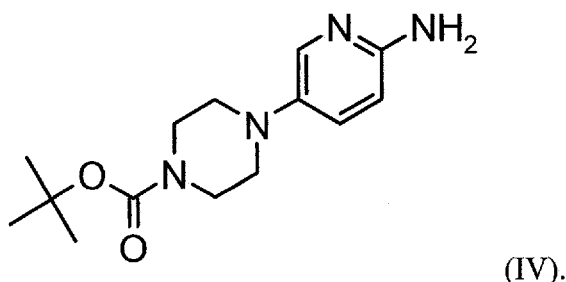
The present invention is also directed to a method of preparing the compound of Formula (II).

The present invention is further directed to a method of preparing the compound of Formula (I).

The present invention is yet further directed to a method of preparing the compound of Formula (III)



The present invention is also further directed a method of preparing the compound of Formula (IV):



The present invention is further directed to pharmaceutical compositions comprising the salt of Formula (II) and at least one pharmaceutically acceptable carrier, diluent, vehicle or excipient.

The present invention is also directed to a method of treating a disease which responds to an inhibition of cyclin dependent kinases, (in particular, cyclin dependent kinases selected from CDK1, CDK2, CDK3, CDK4, CDK5, CDK6 and CDK9) comprising the step of administering to a subject in need of such treatment a therapeutically effective amount of the compound of Formula (II).

Brief Description of the Drawings

Figure 1 shows Dynamic Vapor Sorption (DVS) isotherm plot of Compound of Formula (II) (0-90-0 % Relative Humidity (RH) Cycle).

Figure 2 shows X-ray Powder Diffraction (XRPD) after DVS of Compound of Formula (II) (0-90-0 % RH Cycle).

Figure 3 shows Differential Scanning Calorimetry (DSC) of Compound of Formula (II) after DVS (0-90-0 % RH Cycle).

Figure 4 shows Thermogravimetric Analysis (TGA) of Compound of Formula (II) after DVS (0-90-0 % RH Cycle).

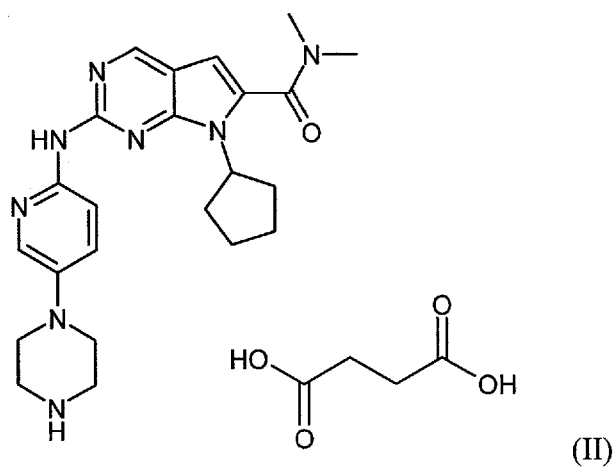
Figure 5 shows DVS isotherm plot of Compound of Formula (II) (0-80-0 % RH Cycle).

Figure 6 shows XRPD after DVS of Compound of Formula (II) (0-80-0 % RH Cycle).

Detailed Description of the Invention

The present invention is directed to succinate salt of 7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide.

The succinate salt is described by Formula (II):



The succinate salt of 7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide can be either in non-hydrate, hydrate forms, or mixtures thereof.

In one embodiment, the succinate salt is greater than 99.9% in the form of non-hydrate.

In one embodiment, the succinate salt is greater than 99% in the form of non-hydrate.

In one embodiment, the succinate salt is greater than 97% in the form of non-hydrate.

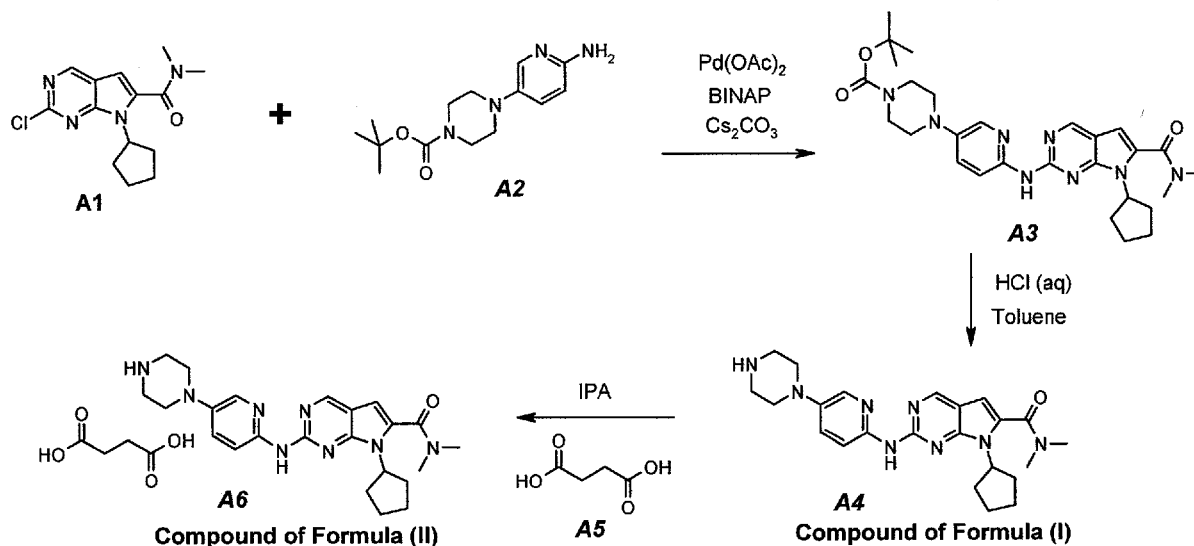
In one embodiment, the succinate salt is greater than 95% in the form of non-hydrate.

In one embodiment, the succinate salt is greater than 90% in the form of non-hydrate.

The non-hydrate form of succinate salt of 7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide has good stability, non-hygroscopicity, and good solubility.

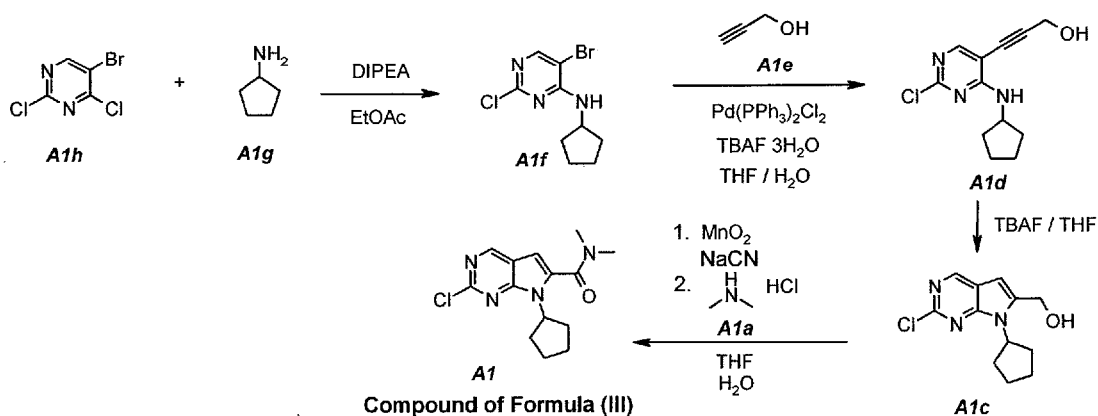
The present invention is also directed to a method of preparing the compound of Formula (I) and the compound of Formula (II):

Process Scheme for Making Compound of Formula (I) and Compound of Formula (II)



The present invention is further directed to a method of preparing the compound of Formula (III):

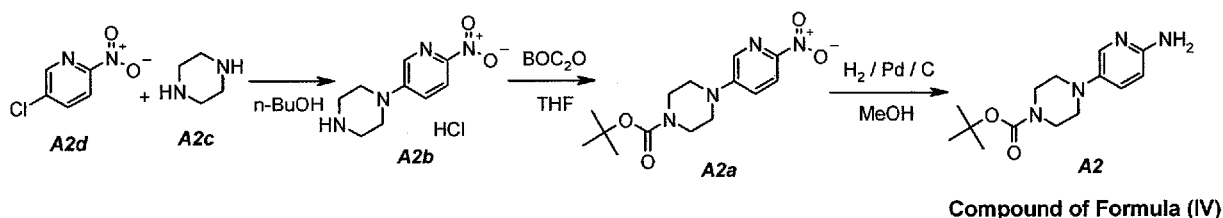
Process Scheme for Making Compound of Formula (III)



Compare to previous method of making the Compound of Formula (III), the present process improved the overall yield of the compound Formula (III) (i.e., **A1**) from 4% to 30%. In addition, the five column purification steps required by the previous method are not needed in this improved process.

The present invention is also further directed a method of preparing the compound of Formula (IV):

Process Scheme for Making Compound of Formula (IV)



In the present synthesis of Compound of Formula (IV) (i.e., A2), a facile method is developed for replacing the chloride in A2d with A2c using *n*-butanol as a solvent. This process increases the yield and avoided chromatographic purification of the Compound of Formula (IV) for further processes.

In summary, a scalable, safer, simpler, higher yielding, and more cost efficient process for manufacturing starting materials A1 (Compound of Formula (III)), A2 (Compound of Formula (IV)), free base A4 (Compound of Formula (I)), and succinate salt A6 (Compound of Formula (II)) is developed. Compare to previous synthesis processes, the overall procedure shortened the synthetic steps and increased the overall yield from 0.9% to 12%.

The present invention is further directed to pharmaceutical compositions comprising the salt of Formula (II) and at least one pharmaceutically acceptable carrier, diluent, vehicle or excipient.

The present invention is also directed to a method of treating a disease which responds to an inhibition of cyclin dependent kinases, (in particular, cyclin dependent kinases selected from CDK1, CDK2, CDK3, CDK4, CDK5, CDK6 and CDK9) comprising the step of administering to a subject in need of such treatment a therapeutically effective amount of the compound of Formula (II).

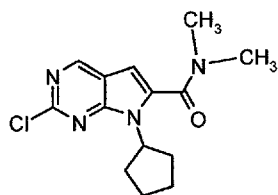
Such disease which responds to an inhibition of cyclin dependent kinases include, but not limited to breast cancer, genitourinary cancer, lung cancer, gastrointestinal cancer, epidermoid

cancer, melanoma, ovarian cancer, pancreas cancer, neuroblastoma, head and/or neck cancer or bladder cancer, or in a broader sense renal, brain or gastric cancer; leukemias, hyperplasias, stomach cancer, colon cancer, larynx cancer, lymphatic system cancer, genitourinary tract cancer, bone cancer, prostate cancer, small-cell lung cancer, glioma cancer, colorectal cancer, kidney cancer, epidermas cancer, liver cancer, esophagus cancer, hematopoietic cancer, lymphoma, myeloma, thyroid follicular cancer; a tumour of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma; a tumour of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xeroderma pigmentosum; keratocanthoma; thyroid follicular cancer; Kaposi's sarcoma, chronic lymphocytic leukaemia, mantle cell lymphoma, large B cell lymphoma.

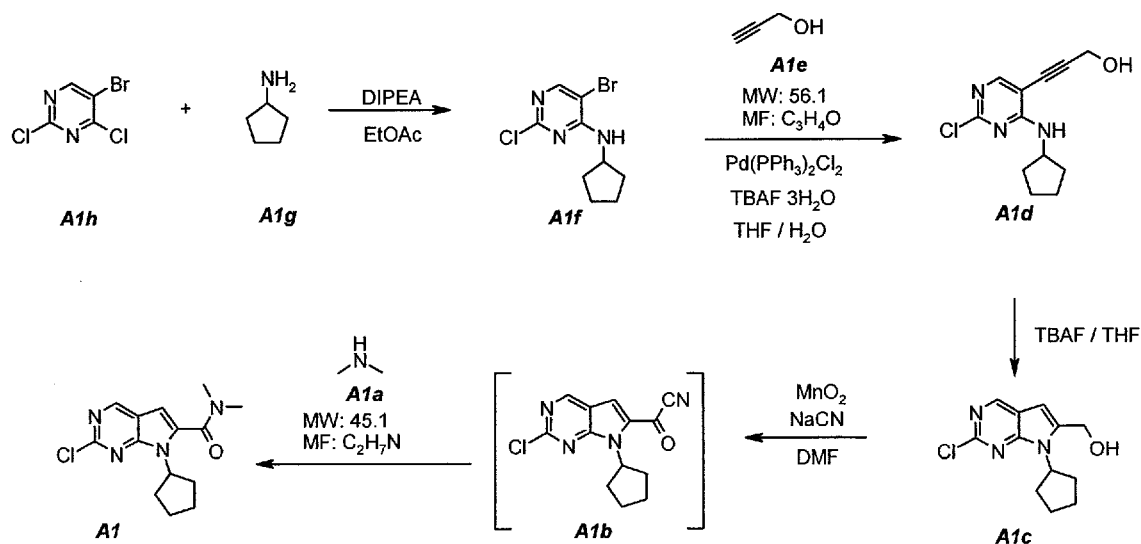
A "therapeutically effective amount" is intended to mean the amount of the inventive salt that, when administered to a subject in need thereof, is sufficient to effect treatment for disease conditions alleviated by the inhibition of cyclin dependent kinases activity. The amount of a given compound of the invention that will be therapeutically effective will vary depending upon factors such as the disease condition and the severity thereof, the identity of the subject in need thereof, etc., which amount may be routinely determined by artisans of ordinary skill in the art.

The "at least one pharmaceutically acceptable carrier, diluent, vehicle or excipient" can readily be selected by one of ordinary skill in the art and will be determined by the desired mode of administration. Illustrative examples of suitable modes of administration include oral, nasal, parenteral, topical, transdermal, and rectal. The pharmaceutical compositions of this invention may take any pharmaceutical form recognizable to the skilled artisan as being suitable. Suitable pharmaceutical forms include solid, semisolid, liquid, or lyophilized formulations, such as tablets, powders, capsules, suppositories, suspensions, liposomes, and aerosols.

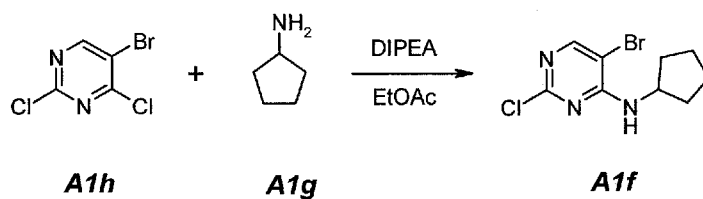
Specific embodiments of the invention will now be demonstrated by reference to the following examples. It should be understood that these examples are disclosed solely by way of illustrating the invention and should not be taken in any way to limit the scope of the present invention.

Example 1 Preparation of Compound A1 (i.e., the Compound of Formula (III)):

Compound A1 (i.e., the Compound of Formula (III), 2-chloro-7-(cyclopentyl-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide) is prepared according to the Synthesis Scheme below.

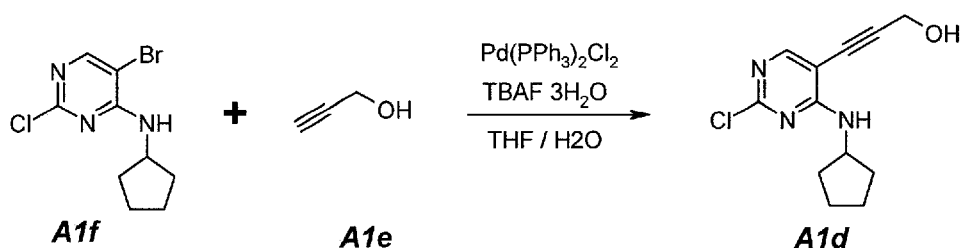
Synthesis Scheme

Details of each of the steps is provided below in Steps 1.1-1.4. Step 1.5 is an optional purification step.

1.1 5-Bromo-2-chloro-N-cyclopentylpyrimidin-4-amine (A1f):

A nitrogen-flushed, suitably equipped 5 L 4-neck round bottom flask is charged with 250 g (1.097 mol, 140.4 mL, 1.0 eq.) of 5-bromo-2,4-dichloropyrimidine (A1h) and 1127 g, (1250 mL) of ethyl acetate. The content is stirred at 20 °C and 283.5 g (2.194 mol, 382.0 mL, 2.0 eq.) of *N,N*-diisopropylethylamine is added. A solution of 102.8 g (1.207 mol, 119 mL, 1.1 eq.) of cyclopentylamine (A1g) dissolved in 1127 g, (1250 mL) of ethyl acetate is added over 60 min. An 18 °C to 36 °C exotherm is observed. The solution is warmed to 40 °C. This temperature is maintained for at least 6 h or until all the starting material A1h, is consumed as determined by HPLC analysis. The resulting slurry is cooled to 25 °C and 500 g (500 mL) of water is added. The content is stirred for 15 min and the phases are allowed to separate. The bottom (aqueous) layer is removed and the organic layer is washed once more with 500 g (500 mL) of water. The sample is stirred for 15 min, and the phases are allowed to separate. The bottom (aqueous) layer is removed. The organic phase is concentrated (atmospheric pressure) to a volume of 1500 mL (batch temp = 82 °C). 684 g (1 L) of heptane is added and the concentration is resumed to a volume of 1500 mL (batch temp = 85 °C). Again, 684 g (1 L) of heptane is added and the concentration is resumed to a volume of 1500 mL (batch temp = 96 °C). The sample is cooled to 50 °C and seeded. The cooling is continued to 4 °C and the temperature is maintained at 4 °C for 1 h. The solids are filtered and the filter cake is washed once with 137 g (200 mL) of cold (4 °C) heptane. The solids are dried at 50 °C for 16 h, to afford 259.0 g (88.0%, corrected) of Compound A1f as a white, crystalline solid, mp = 95 – 96 °C.

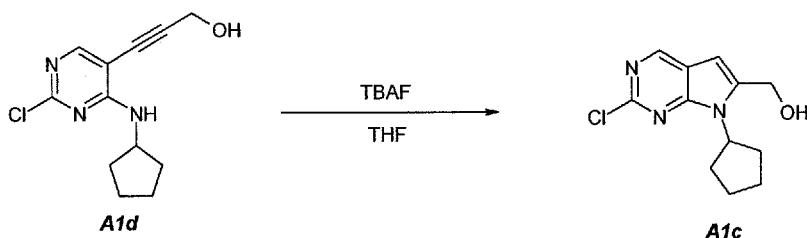
1.2 3-[2-Chloro-4-(cyclopentylamino)pyrimidin-5-yl]prop-2-yn-1-ol (A1d)



A nitrogen-flushed, suitably equipped 5 L 4-neck round bottom flask is charged with 200 g (0.723 mol, 1.0 eq.) of 5-bromo-2-chloro-*N*-cyclopentylpyrimidin-4-amine (A1f) and

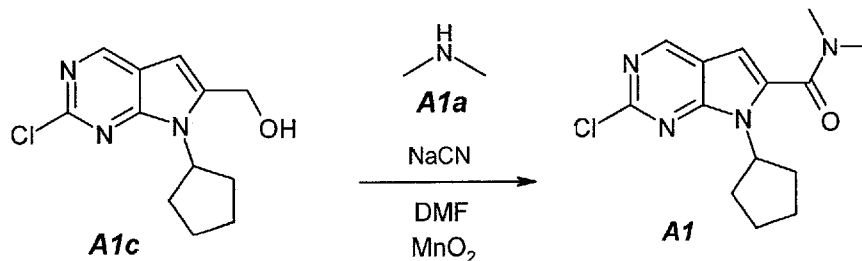
2303 g, (2600 mL) of tetrahydrofuran. The mixture is stirred, heated to reflux (67 °C) and 200 mL of distillate is collected. The sample is cooled to 25 °C and 52.7 g (0.940 mol, 55.6 mL, 1.3 eq.) of propargyl alcohol (A1e), 570.3 g (1.808 mol, 2.5 eq.) of tetrabutylammonium fluoride trihydrate and 25.4 g (0.036 mol, 0.05 eq.) of bis(triphenylphosphine)palladium (II) dichloride are added. The sample is stirred, heated to reflux (67 °C) and maintained at this temperature for 2 h or until 5–7% of the starting material A1f remains as determined by HPLC analysis. The sample is cooled to 25 °C and concentrated under reduced pressure (100 mbar, 30 °C maximum internal temperature) to a volume of 1150 mL to remove tetrahydrofuran. 541 g, (600 mL) of ethyl acetate is charged. The sample is again concentrated under reduced pressure (100 mbar, 30 °C maximum internal temperature) to a volume of 1150 mL to remove residual tetrahydrofuran. 2706 g (3000 mL) of ethyl acetate and a solution of 63 g of sodium bicarbonate dissolved in 1500 g (1500 mL) of water are added. The sample is stirred at 25 °C for 10 min and the phases are separated. The organic (top) phase is washed once with 1500 g (1500 mL) of water. The sample is stirred for 10 min and the phases are separated. The organic (top) phase is concentrated under reduced pressure (100 mbar, 30 °C maximum internal temperature) to a volume of 625 mL to remove ethyl acetate. 1582 g (2000 mL) of acetone is added to the concentrate. The sample is stirred, heated to reflux (58 °C) and maintained at this temperature for 30 min. It is then cooled to 40 °C and clarified by filtering through a pad of filter cel. The flask and filter cake are washed twice with 158 g (200 mL, 2 x 100 mL per wash) of acetone. The sample is concentrated under reduced pressure (100 mbar, 30 °C maximum internal temperature) to a volume of 460 mL. It is then cooled to 4 °C and is hold at this temperature for 1 h. The solids are filtered and the filter cake is washed twice with 158 g (2 x 100 mL) of cold (4 °C) acetone. The solids are dried at 50 °C for 16 h, to afford 85.6 g (47.4%, corrected) of Compound A1d as a tan, crystalline solid, mp = 162 – 163°C.

1.3 (2-chloro-7-cyclopentyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl)methanol (A1c)



A dry nitrogen-flushed 5 L 4-neck round bottom flask is charged with 100 g (Purity: 98%, 0.389 mol 1.0 eq.) of 3-(2-chloro-4-(cyclopentylamino)pyrimidin-5-yl)prop-2-yn-1-ol, (A1d), 880 g (1000 mL) of peroxide free tetrahydrofuran and 753 g, (856 mL) of tetrabutylammonium fluoride, 1.0M solution in THF. The content is stirred at 25 °C for 10 min, and then the solution is warmed to 60 °C. This temperature is maintained for 1.5 h until the starting material, A1d, is $\leq 2.5 \pm 0.5\%$ as determined by HPLC analysis. The resulting solution is cooled to below 30 ± 3 °C², and distilled under reduced pressure to remove THF. 79 g (100 mL) of 2-propanol is added. The sample is stirred for 15 min and 1000 g (1000 mL) of water then add slowly over 30 min. The sample is stirred at 20 ± 3 °C for 30 min and then filtered. The cake is washed twice with 200 g (2 x 100 mL) of water. The solids are dried at 50 °C for 16 h to afford Compound A1c as a tan, crystalline solid, mp = 174 – 176°C.

1.4 2-Chloro-7-cyclopentyl-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A1)



A dry, nitrogen-flushed ACE-100L Reaction vessel is charged with 97.3 g of sodium cyanide, 2,500 g of (2-chloro-7-cyclopentyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)methanol, A1c, 16,680 g (19.5 L) of dimethylamine, A1a (2.0M solution in THF), and 28,320 g (30,0 L) of anhydrous N,N-dimethylformamide. The mixture is stirred at 20 ± 3 °C for 15 min. 2.06 kg of manganese(IV) oxide is then added. The dark slurry is stirred for 30 min and 12.36 Kg of manganese (IV) oxide is added in three portions (1st portion: 2.06 kg; 2nd portion: 4.12 g, and 3rd portion: 6.18 kg) every 30 min. After the last portion has been added, the sample is held for 1h and then 6.18 kg of manganese(IV) oxide is added. The sample is held for 1 h. The reaction mixture is then sampled. The reaction is considered complete if the starting material, A1c is $\leq 1.0 \pm 0.5\%$ as determined by HPLC analysis. The reaction mixture is then filtered through a pad of celite to remove manganese (IV) oxide. The reactor and cake are rinsed with 23 L of ethyl acetate. The filtrate and distil are combined under reduced pressure (45 ± 3 °C, 20 mbar) to remove THF, dimethylamine and ethyl acetate. The sample is further distilled under reduced pressure (70 ± 5 °C, 5 mbar) to remove DMF. The concentrate is diluted with 35 L of ethyl acetate. The resulting dark solution is washed with aqueous ferrous sulfate solution (1 kg of FeSO₄·7H₂O in 14 L of water), 15 L of water and finally 15 L of 10% aqueous NaCl solution. The phases are separated after each wash. The organic phase is distilled (45 °C, 50 mbar) to azeotropically remove water. The resulting crude A1 (2,788 g of a dark, thick, semi-solid residue) can be used directly in the next step.

1.5 Procedure: Isolation of pure A1 from crude A1:

Optionally the crude A1 from step 1.4 can be purified by either Method 1 or 2 below.

Method-1:

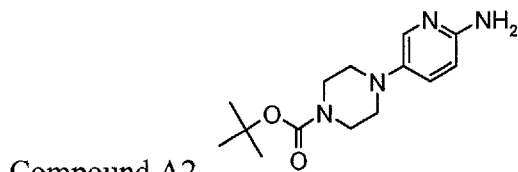
10 g of crude A1 and 9 mL of 1-propanol are warmed gently until a homogeneous, dark solution is obtained. The solution is cooled to 25 ± 3 °C and 30 to 40 mL of hexane is slowly added. The sample is seeded and stirred until crystals are observed. An additional 50 to 60 mL of hexane is slowly added. The total volume of hexane added is about 90 mL. The slurry is held at 22 ± 3 °C for 2 h, then cooled to 4 °C and held for an additional 2 h. The solids are filtered. The flask and filter cake are washed with hexane as needed. The filter

cake is dried at 50 °C, 50 mbar to afford 6.35 g of purified A1 as a light tan, crystalline solid. Recovery: 63.5%.

Method 2:

A solution of 10 g of crude A1 in 10 mL of EtOAc is prepared and loaded onto a 100 g bed of silica gel. The column is eluted with 300 mL of EtOAc / hexane (2/8) and the eluant is discarded. The column is then eluted with 800 mL of EtOAc/hexane (5/5) and the eluant is collected (#2) for isolation of the product. The eluant (#2) is concentrated to thin oil. 100 mL of hexane is slowly added and the sample is stirred at 22 ± 3 °C for 2 h. The sample is cooled to 4 °C and held an additional 2 h. The solids are filtered. The flask and filter cake are washed with hexane as needed. The filter cake is dried at 50 °C, 50 mbar to afford 6.05 g of purified A1 as a light tan, crystalline solid. Recovery 60.5%.

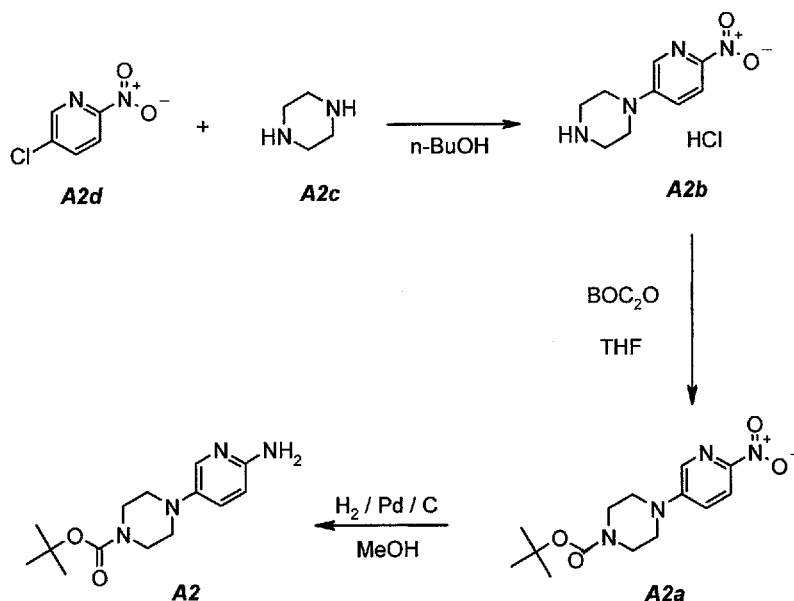
Example 2 Preparation of Compound A2 (i.e., the Compound of Formula (IV), *tert*-butyl 4-(6-aminopyridin-3-yl)piperazine-1-carboxylate):



(i.e., the Compound of Formula (IV), *tert*-butyl

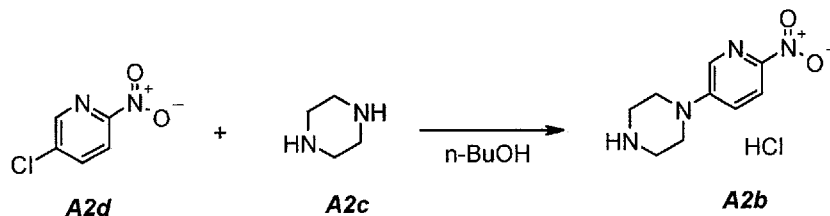
4-(6-aminopyridin-3-yl)piperazine-1-carboxylate) is prepared according to the Synthesis Scheme below.

Synthesis Scheme



Details of each of the steps is provided below in Steps 2.1-2.4.

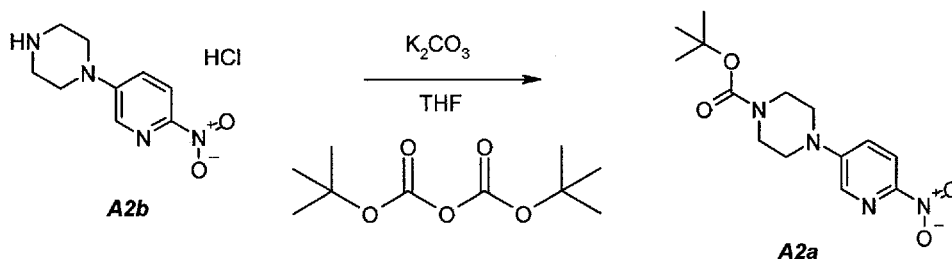
2.1 1-(6-Nitropyridin-3-yl)piperazine hydrochloride (A2b)



A nitrogen-flushed, suitably equipped 22 L 4-neck round bottom flask is charged with 1392 g (8.78 mol, 1.0 eq.) of 5-chloro-2-nitropyridine (**A2d**), 1512 g (17.56 mol, 2.0 eq.) of piperazine (**A2c**) and 11,340 g (14,000 mL) of *n*-butanol. The resulting suspension is stirred and heated to 95 °C. This temperature is maintained for at least 24 h or until the remaining starting material, **A2d**, is $\geq 2\%$ (area normalization) as determined by HPLC analysis. The resulting slurry is cooled to 25 °C over 1 h. The solids are filtered through a polypropylene filter pad. The filter cake is washed twice with a total of 2267 g (2 x 1300 mL) of isopropyl

acetate. The solids are dried at 60 °C for 16 h, to afford 1769 g (82.3%, uncorrected) of A2b as a yellow, crystalline solid, mp >230 °C (dec.).

2.2 *tert*-Butyl 4-(6-Nitropyridin-3-yl)piperazine-1-carboxylate (A2a)

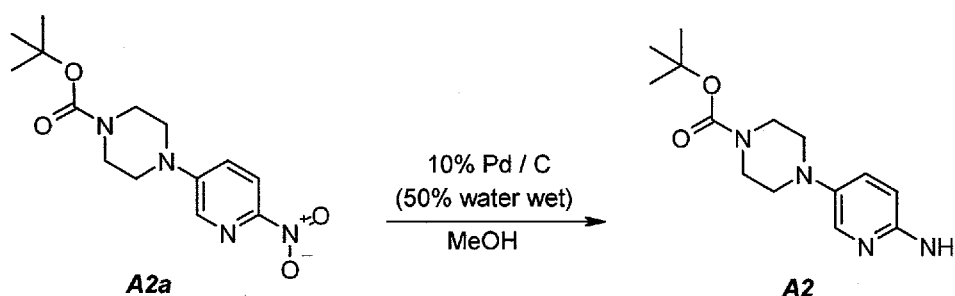


A nitrogen-flushed, suitably equipped 22 L 4-neck round bottom flask is charged with 589 g (2.41 mol, 1.0 eq.) of 1-(6-nitropyridin-3-yl)piperazine hydrochloride (A2b). A solution of 630.5 g (2.89 mol, 1.2 eq.) of di-*tert*-butyl dicarbonate in 10,223 g (11,500 mL) of tetrahydrofuran is prepared and charged to the flask. The resulting suspension is stirred and cooled to 8 ± 3 °C. A nitrogen-flushed, suitably equipped 5 L 4-neck round bottom flask is charged with 499 g (3.61 mol, 1.5 eq.) of potassium carbonate. 3,600 g (3,600 mL) of water is added to the 5 L flask. After stirring a solution is obtained. This solution is cooled to 25 ± 3 °C and transferred to the reaction mixture over 30 min. A batch temperature ≤ 12 ± 3 °C is maintained throughout the addition. The mixture is warmed to 22 ± 3 °C and held at this temperature for an additional 1 h or until the starting material, A2b, is no longer visible as determined by TLC analysis. The 2-phase mixture is filtered through a 250 g pad of Celite. The filter cake is washed twice with a total of 800 g (2 x 450 mL) of tetrahydrofuran. The wash is combined with the filtrate. The phases are separated and the aqueous (bottom) phase is discarded. The filtrate is concentrated under reduced pressure (100 mbar, 40 °C internal MAXIMUM.) to a thick paste.

This entire process are repeated twice more. The concentrates from all three runs are combined in a nitrogen-flushed, suitably equipped 22 L 4-neck round flask. 4,719 g (6,900 mL) of heptane is charged to the concentrated batches. The sample is stirred and concentrated under reduced pressure (100 mbar, 40 °C internal MAXIMUM.) to a thick paste. Again, 3,146 g (4,600 mL) of heptane is charged to the concentrated batch. The resulting suspension is stirred at 37 ± 3 °C for 1 h; cooled to 22 ± 3 °C, held for 15 min. The solids are

filtered through a polypropylene filter pad and washed twice with 615 g (2 x 450 mL) of heptane. The solids are dried at 55 °C with a nitrogen sweep² for 16 h, to afford 2,088 g (93.8%) of Compound A2a as a yellow, crystalline solid, mp 173–174 °C.

2.3 *tert*-Butyl 4-(6-Aminopyridin-3-yl)piperazine-1-carboxylate (A2)



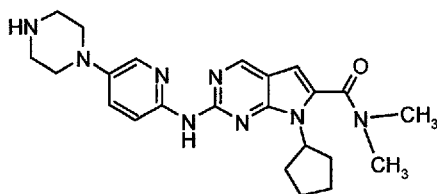
A nitrogen-flushed, 2.5 L heavy-wall Parr bottle (pressure rated to 60 psi) is charged with 68 g (0.22 mol,) of *tert*-butyl 4-(6-nitropyridin-3-yl)piperazine-1-carboxylate, (A2a), 6.8 g of 10% palladium on carbon, 50% water wet catalyst and 807 g (1020 mL) of methanol. The reaction vessel is inerted three times with nitrogen (ca. 30 psi), evacuating the atmosphere above the reaction mixture each time. The vessel is pressurized twice with hydrogen (ca. 30 psi), evacuating the atmosphere above the reaction mixture each time. The reaction vessel is pressurized to 45 psi with hydrogen. The shaker motor is started. The reaction is exothermic. A temperature rise from 19 to 54 °C over 15 min is observed after which time the hydrogen uptake stops. The mixture is allowed to cool to 30 °C over 1 h at which point the shaker is stopped. The hydrogen atmosphere is replaced with nitrogen as described above (Inert the reaction vessel). The catalyst is removed by filtration through a 10 g pad of filter cel. This entire process is repeated once more, both filtrates are combined and charged to a clean 3 L 4-neck round bottom flask.

2.4 Product isolation.

The filtrates from Step 2.3 is stirred and concentrated under reduced pressure (50 mbar, 40 °C internal MAXIMUM.) to a thick paste. 190 g (250 mL) of *tert*-butyl methyl ether is charged to the residue. The sample is again stirred and concentrated under reduced pressure (50 mbar,

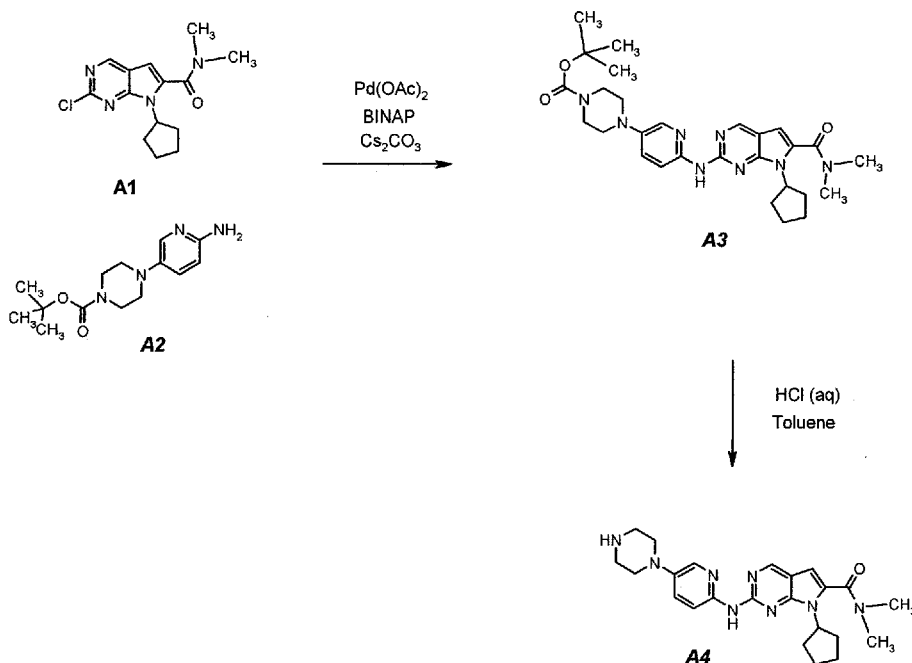
30 °C internal MAXIMUM.) to a thick paste. 342 g (500 mL) of heptane is charged to the residue and the resulting suspension is stirred for 15 min at 22 ± 3 °C. The solids are filtered and the filter cake is washed with 68 g (100 mL) of heptane. Dry the solids at 50 °C for 16 h, to afford 112.3 g (93.4%) of Compound A2 as tan plates, mp 124 – 126 °C.

Example 3 Preparation of 7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide (i.e., the Compound of Formula (I)):



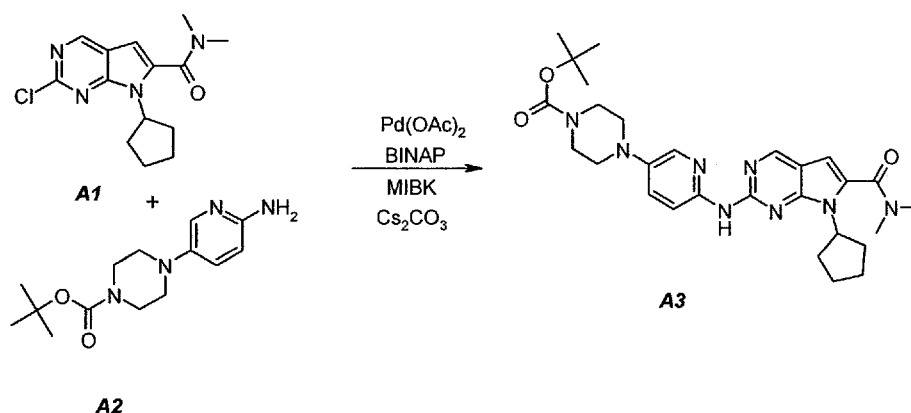
Compound A4 (i.e., the Compound of Formula (I), 7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide) is prepared according to the Synthesis Scheme below.

Synthesis Scheme:



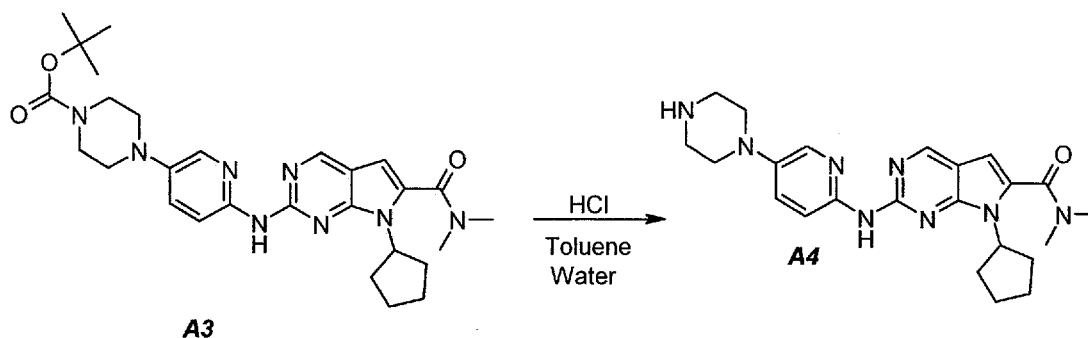
Details of each of the steps is provided below in Steps 3.1-3.2.

3.1 tert-Butyl 4-(6-(7-cyclopentyl-6-(dimethylcarbamoyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)pyridin-3-yl)piperazine-1-carboxylate (A3):



A nitrogen-flushed, 3 L, Argonaut reactor system is charged with 43.9 g (0.15 mol, 1.0 eq) of 2-chloro-7-cyclopentyl-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide, (crude A1, from Step 1.4 above), 45.9 g (0.165 mol, 1.1 eq.) of *tert*-butyl 4-(6-aminopyridin-3-yl)piperazine-1-carboxylate (A2), 0.67 g (3.0 mmol, 0.02 eq) of palladium (II) acetate, 3.73 g (6.0 mmol, 0.04 eq) of ($\pm$) 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene, $\pm$ BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) and 275 g (344 mL) of 4-methyl-2-pentanone. The resulting suspension is stirred and heated to 40 ± 3 °C. 73.3 g (0.225 mol, 1.5 eq) of cesium carbonate is added in 5 to 10 g portions over 15 min. The resulting suspension is stirred and heated to 100 ± 3 °C. This temperature is maintained for 3h or until the remaining starting material, A1, is $\leq 2\%$ (area normalization) as determined by HPLC analysis. The progress of the reaction is checked using the Process Steering Control. The sample is cooled to 70 ± 3 °C and 344 g (344 mL) of water is added over 5 min. The sample is cooled to 50 ± 3 °C and held at this temperature for 30 min. 353 g (516 mL) of heptane is added over 30 minutes and the sample is stirred for 2 h. The mixture is then cooled to 22 ± 3 °C and held at least 4 h (hold point). The solids are filtered through a polypropylene filter pad. The filter cake is washed with a cold (4 °C) mixture of 24 g (30 mL) of 4-methyl-2-pentanone and 41 g (60 mL) of heptane. The solids are dried at 60 °C until HSGC PSC shows organic solvents to be $\leq 1\%$, to afford 72.6 g of A3 as a tan solid mp 215–217 °C (dec.).

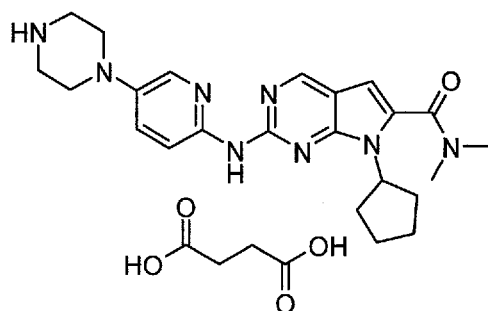
3.2 7-Cyclopentyl-N,N-dimethyl-2-(5-(piperazin-1-yl)pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A4):



A nitrogen-flushed, 3 L Argonaut reactor system is charged with 67.4 g (0.126 mol, 1.0 eq.) of *tert*-Butyl 4-(6-(7-cyclopentyl-6-(dimethylcarbamoyl)-7H-pyrrolo[2,3-*d*]pyrimidin-2-ylaminopyridin-3-yl)piperazine-1-carboxylate (A3) and 329 g (380 mL) of toluene. The suspension is stirred and cooled to 12 ± 3 °C. 138 g (126 mL, 6.0 eq) of 6N aqueous hydrochloric acid is added over 30 min maintaining a batch temperature $\leq 15 \pm 3$ °C. The resulting 2-phase solution is warmed to 25 ± 3 °C and held at this temperature for 30 min or until the remaining starting material, A3, is $\leq 2\%$ (area normalization) as determined by HPLC analysis. The progress of the reaction is checked using the Process Steering Control. 250 g (250 mL) of 1N aqueous hydrochloric acid is added and mixture is stirred for 5 min. The 2-phase reaction mixture is filtered through 25 g of filter cel. The phases are separated. The aqueous phase (containing product) is charged to a 2 L, 4-neck, round bottom flask (equipped as described under Apparatus entry 4) and cooled to 15 ± 3 °C. The pH is adjusted to 3.2 ± 0.3 with the slow addition of 62 g (41 mL) of 50% aqueous sodium hydroxide, a batch temperature $\leq 27 \pm 3$ °C is maintained throughout the addition. 16.4 g of Si-Thiol functionalized silica gel is added. The slurry is stirred for 3 hours at 50 ± 3 °C. The resin is filtered off, the flask and filter cake are rinsed with 50 mL of water. The wash is combined with the filtrate. The filtrate is transferred back to the flask and 16.4 g of Si-Thiol functionalized silica gel is added. The slurry is stirred for 3 hours at 50 ± 3 °C. The silica gel is filtered off. The flask and filter cake are rinsed with 50 mL of water. The wash is combined with the filtrate. The filtrate is transferred back to the flask and again 16.4 g of Si-Thiol functionalized silica gel is added. The slurry is stirred for 3 hours at 50 ± 3 °C. The

silica gel is filtered off. The flask and filter cake are rinsed with 50 mL of water. The wash is combined with the filtrate. A nitrogen-flushed, 3 L, Argonaut reactor system is charged with the filtrate and cooled to 15 ± 3 °C. The pH is adjusted to 12.5 ± 0.5 with the slow addition of 17 g (18 mL) of 50% aqueous sodium hydroxide to precipitate the product (Batch volume = 900 mL, Max Vol). The sample is stirred for at least 6 h at 22 ± 3 °C. The solids are filtered through a polypropylene filter pad. The filter cake is washed four times with 340 g (4 x 85 mL) of water until the pH of the wash is ≤ 9 . The solids are dried at 60 °C for at least 16 h or until the LOD is $\leq 1\%$ to afford 45.7 g (84.9%, corrected) of compound A4 as a tan solid, mp 194–195 °C.

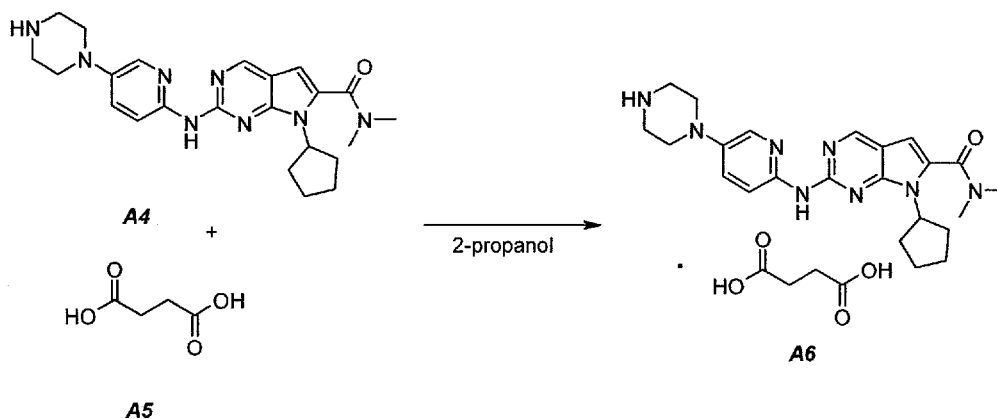
Example 4 Preparation of the Succinate salt of 7-Cyclopentyl-2-(5-piperazin-1-ylpyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide (i.e., Compound A6, the Compound of Formula (II)):



Compound A6

(i.e., the Compound of Formula (II),

7-Cyclopentyl-*N,N*-dimethyl-2-(5-(piperazin-1-yl)pyridin-2-ylamino)-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide succinate) is prepared according to the Synthesis Scheme below.



A nitrogen-flushed, 1 L, 4-neck, round bottom flask is charged with 11.16 g (0.0945 mol, 1.05 eq.) of succinic acid (A5), and 245 g (312 mL) of 2-propanol. The suspension is stirred and warmed to 65 ± 3 °C to obtain a clear solution. The solution is filtered while warmed through glass-fiber filter paper. The filtrate is held at 30 ± 3 °C for addition to A4. A nitrogen-flushed 2 L, 4-neck, round bottom flask is charged with 39.11 g (0.09 mol, 1.0 eq) of 7-cyclopentyl-*N,N*-dimethyl-2-(5-(piperazin-1-yl)pyridin-2-ylamino)-7*H*-pyrrolo[2,3-*d*] pyrimidine-6-carboxamide (A4) and 1115 g (1420 mL) of 2-propanol. The resulting suspension is stirred and heated to 80 ± 3 °C to obtain a hazy yellow solution. The solution is cooled to 70 ± 3 °C and filtered through a 25 g pad of Celite. The warm, filtered A4 solution is transferred to a nitrogen-flushed, 3 L, Argonaut reactor system and re-heated to 80 ± 3 °C. The succinic acid / 2-propanol solution is added over 1 h maintaining 80 ± 3 °C throughout the addition. The batch is seeded after 80% of the succinic acid solution has been added. The sample is stirred at 80 ± 3 °C for 1 h after the addition is completed and cooled to 20 ± 3 °C over 1 h, held 30 minutes and the solids are filtered. The filter cake is washed with 78 g (100 mL) of 2-propanol. The solids are dried at 60 °C for at least 16 h or until the LOD is $\leq 1\%$ to afford 47.16 g (94.9%, corrected) of Compound A6 as a yellow, crystalline solid, mp 202–203 °C.

Example 5 **Physical Form Characterization of the Compound of Formula (II) under 90% RH:**

To understand its hygroscopic nature, Compound A6 obtained in Example 4 is exposed to two moisture cycle of 0 to 90 to 0 % RH. Table 1 and Figure 1 shows the Compound A6 absorbs up to 2 % moisture at 90% RH in each cycle, reflecting slight hygroscopic behavior at high humidity conditions. Also a steep rise in moisture absorption is observed at 90% RH condition in each cycle and difference in sorption and desorption behavior reflects a formation of hydrate form is taking place at 90% RH condition. Figures 2, 3 and 4 show change in physical form up on exposure to 90% RH for the compound A6 as a different crystalline form is observed with a endothermic transition which shows a weight loss of 3% around 100°C, both of which conversion to a hydrate form after exposure to 90% RH.

At 90% RH, about 7.35% of the Compound A6 obtained in Example 4 is converted from the non-hydrate form to hydrate form.

Example 6 Physical Form Characterization of the Compound of Formula (II) under 90% RH:

To confirm that the form change observed under 90% RH is not taking place at 80% RH, compound A6 obtained in Example 4 is exposed to a moisture cycle of 0 to 80 to 0 % RH. Table 2 and Figure 5 shows Compound A6 absorbs up to 0.5% moisture at 80% RH reflecting nearly non-hygroscopic behavior at 80 °C. Figures 5 and 6 show stability of the physical form of Compound of Formula (II) up on exposure to 80% RH which is reflective of non-hydrate form. Since for stability of drug substance and drug product a physical form stability at 75% RH is desirable, Compound of Formula (II) (non-hydrate) is suitable for development.

At 80% RH, only about 0.52% of the Compound A6 obtained in Example 4 is converted from the non-hydrate form to hydrate form.

Example 7 Solubility:

The solubility of the non-hydrate form in water is about 30 mg/ml. In contrast, the solubility of the hydrate form is significantly lower and is less than 0.5 mg/ml.

Table 1 Isotherm table of Compound of Formula (II) (0-90-0 % RH Cycle)

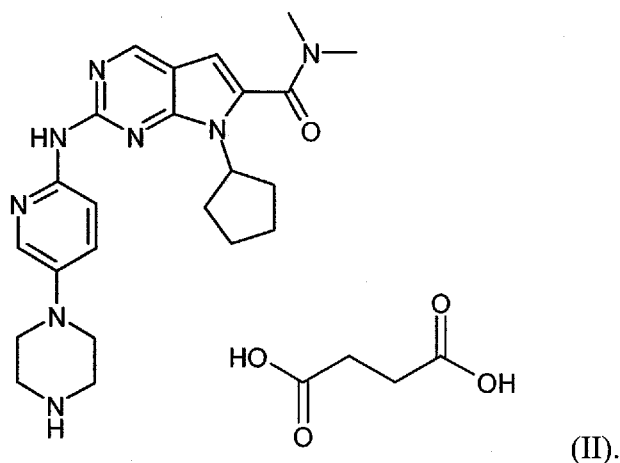
	Target RH (%)	Change In Mass (%) - ref		
		Sorption	Desorption	Hysteresis
Cycle 1	0.0	0.002	0.348	
	10.0	0.110	1.721	1.611
	20.0	0.156	1.977	1.821
	30.0	0.201	2.140	1.939
	40.0	0.222	2.254	2.032
	50.0	0.242	2.332	2.090
	60.0	0.261	2.403	2.142
	70.0	0.250	2.466	2.216
	80.0	0.251	2.514	2.262
	90.0	2.503	2.503	
Cycle 2	0.0	0.348	0.441	
	10.0	1.617	2.634	1.017
	20.0	1.904	3.004	1.100
	30.0	2.078	3.216	1.138
	40.0	2.207	3.378	1.170
	50.0	2.303	3.492	1.188
	60.0	2.377	3.593	1.215
	70.0	2.426	3.675	1.249
	80.0	2.474	3.750	1.277
	90.0	3.808	3.808	

Table 2 Isotherm table of Compound of Formula (II) (0-80-0 % RH Cycle)

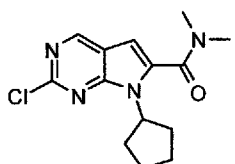
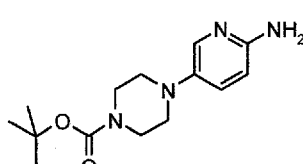
Cycle	Target RH (%)	Change In Mass (%)		
		Sorption	Desorption	Hysteresis
1	0.0	0.0019	0.0434	
	10.0	0.2087	0.2958	0.0871
	20.0	0.2728	0.3436	0.0708
	30.0	0.3597	0.3806	0.0209
	40.0	0.3904	0.4037	0.0133
	50.0	0.4237	0.4311	0.0074
	60.0	0.4474	0.4614	0.0140
	70.0	0.4793	0.4952	0.0159
	80.0	0.5200	0.5200	

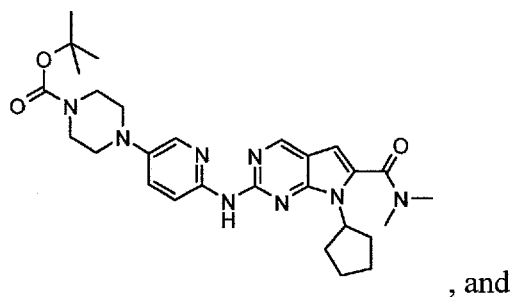
WHAT IS CLAIMED IS:

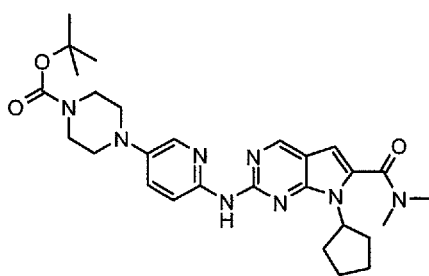
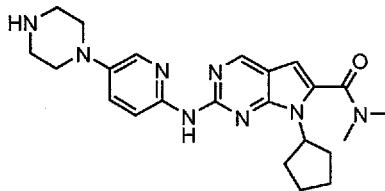
1. Succinate salt of 7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide.
2. The salt of Claim 1, wherein the salt is described by Formula (II)



3. The salt of Claim 1 in a non-hydrate form.
4. The salt of Claim 1 in a hydrate form.
5. A pharmaceutical composition comprising:
 - (a) a therapeutically effective amount of a salt according to any of claims 1-4; and
 - (b) at least one pharmaceutically acceptable carrier, diluent, vehicle or excipient.
6. A method of treating a disease which responds to an inhibition of cyclin dependent kinases activity comprising the step of administering to a subject in need of such treatment a therapeutically effective amount of a salt according to any of claim 1-4.
7. A method of preparing the compound of Formula (I) comprising

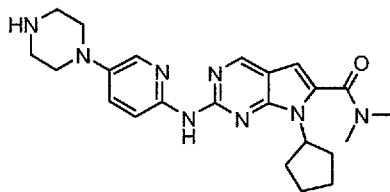
(1) reacting  and  to form

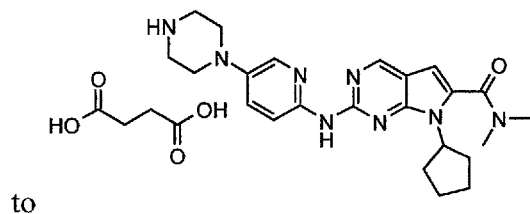


(2) converting the  to .

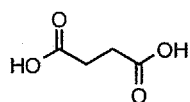
8. The method of claim 7, wherein step (1) is performed in the presence of $\text{Pd}(\text{OAc})_2$, BINAP, and Cs_2CO_3 .

9. The method of claim 7, wherein step (2) is performed in the presence of $\text{HCl}(\text{aq.})$ and toluene.

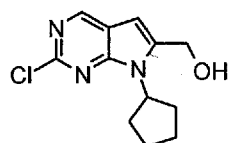
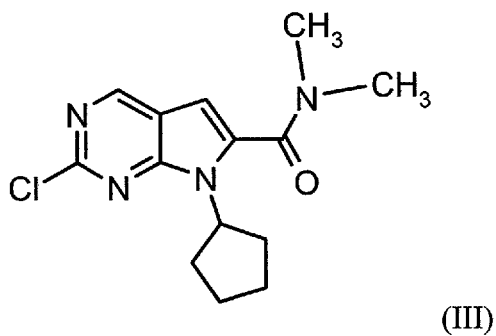
10. The method of claim 7, wherein the  is further converted



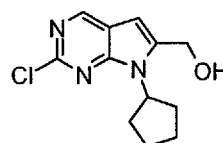
11. The method of claim 10 where in the conversion takes place in the presence of IPA and

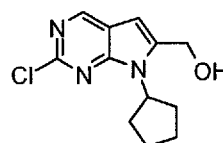
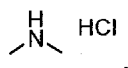


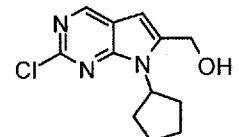
12. A method of preparing the compound of Formula (III):

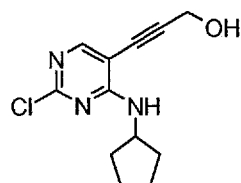


comprising converting

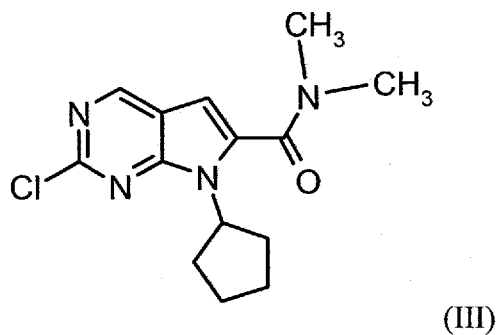


13. The method of claim 12, wherein the conversion of the  takes place in the presence of MnO₂, NaCN, , and THF.

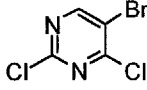
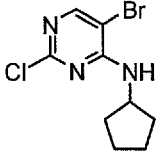
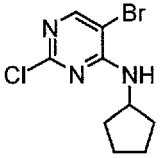
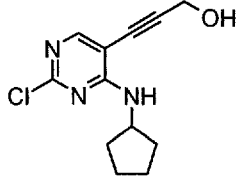
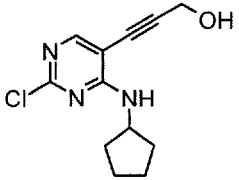
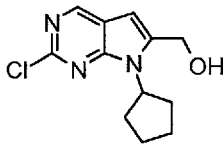
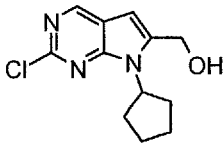
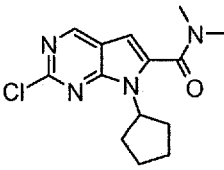
14. The method of claim 12 wherein the  is formed from



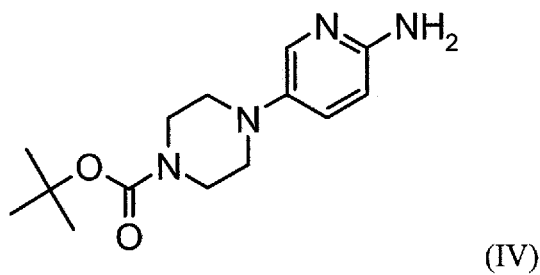
15. A method of preparing the compound of Formula (III):



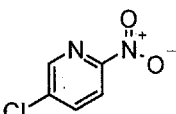
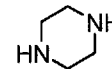
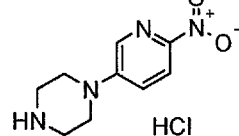
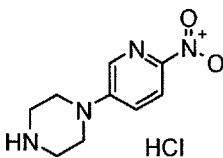
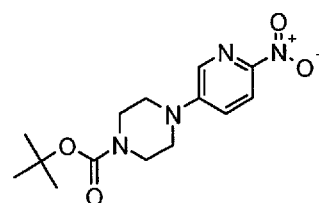
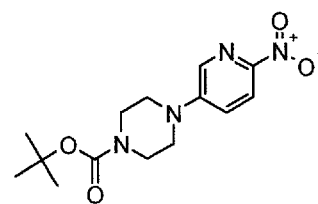
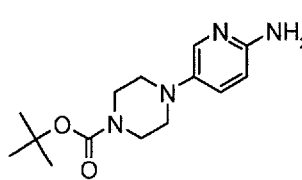
comprising:

- (1) reacting  and  to form ,
- (2) converting the  to form ,
- (3) converting the  to form , and
- (4) converting the  to form .

16. A method of preparing the compound of Formula (IV):

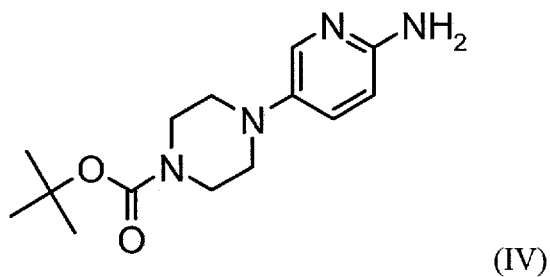


comprising

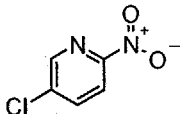
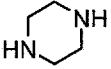
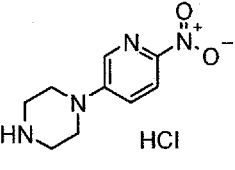
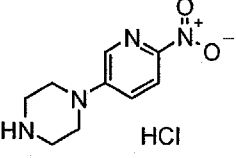
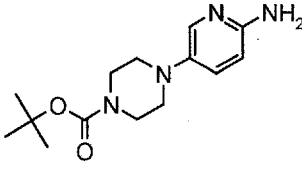
- (1) reacting  with  to form  ,
- (2) converting the  to form  , and
- (3) converting the  to form  .

17. The method of claim 16 wherein the reaction takes place in the presents of n-BuOH.

18. A method of preparing the compound of Formula (IV):



comprising:

- (1) reacting  with  to form  HCl, and
- (2) further converting the  HCl to form .

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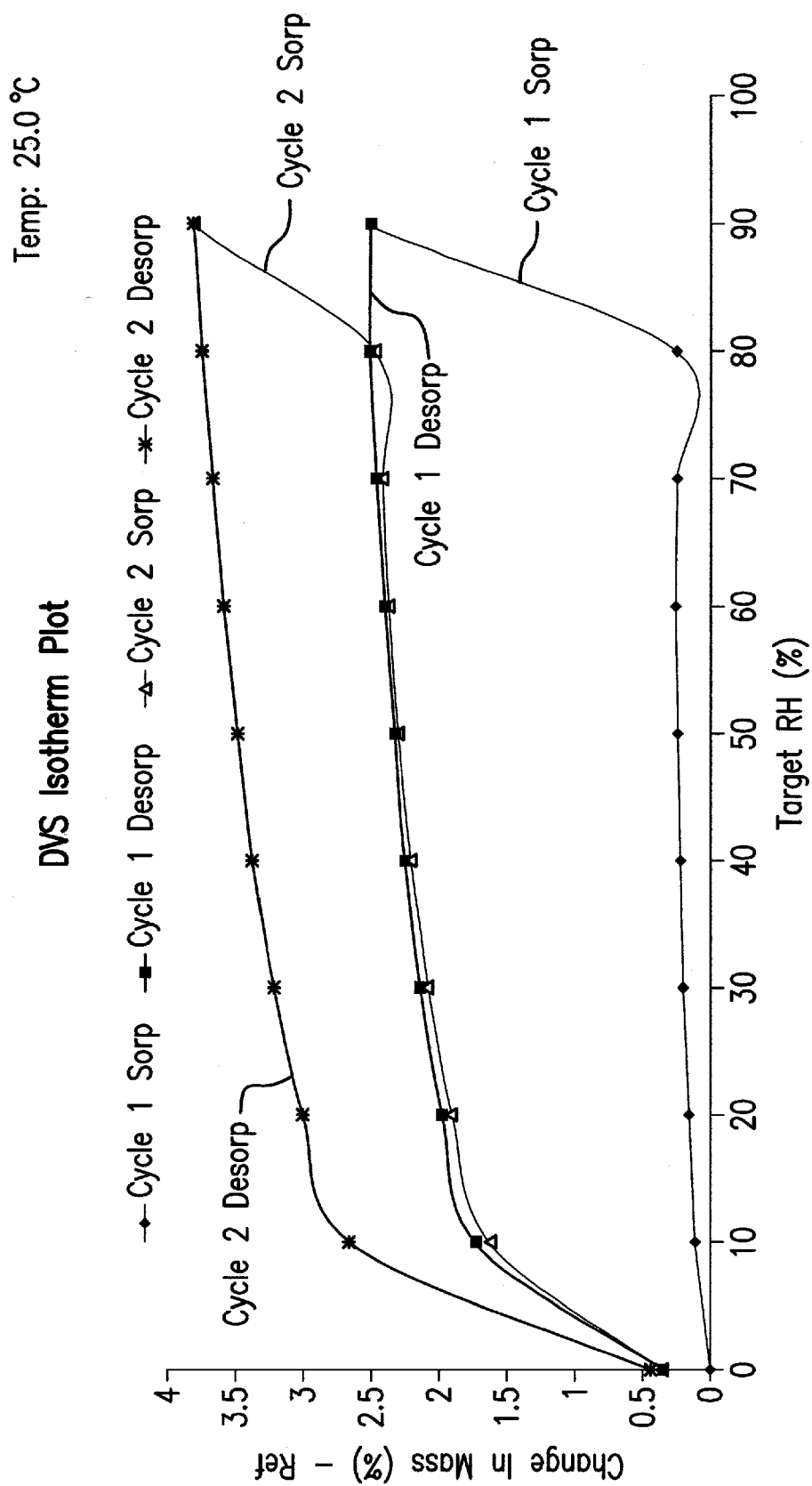


FIG.1

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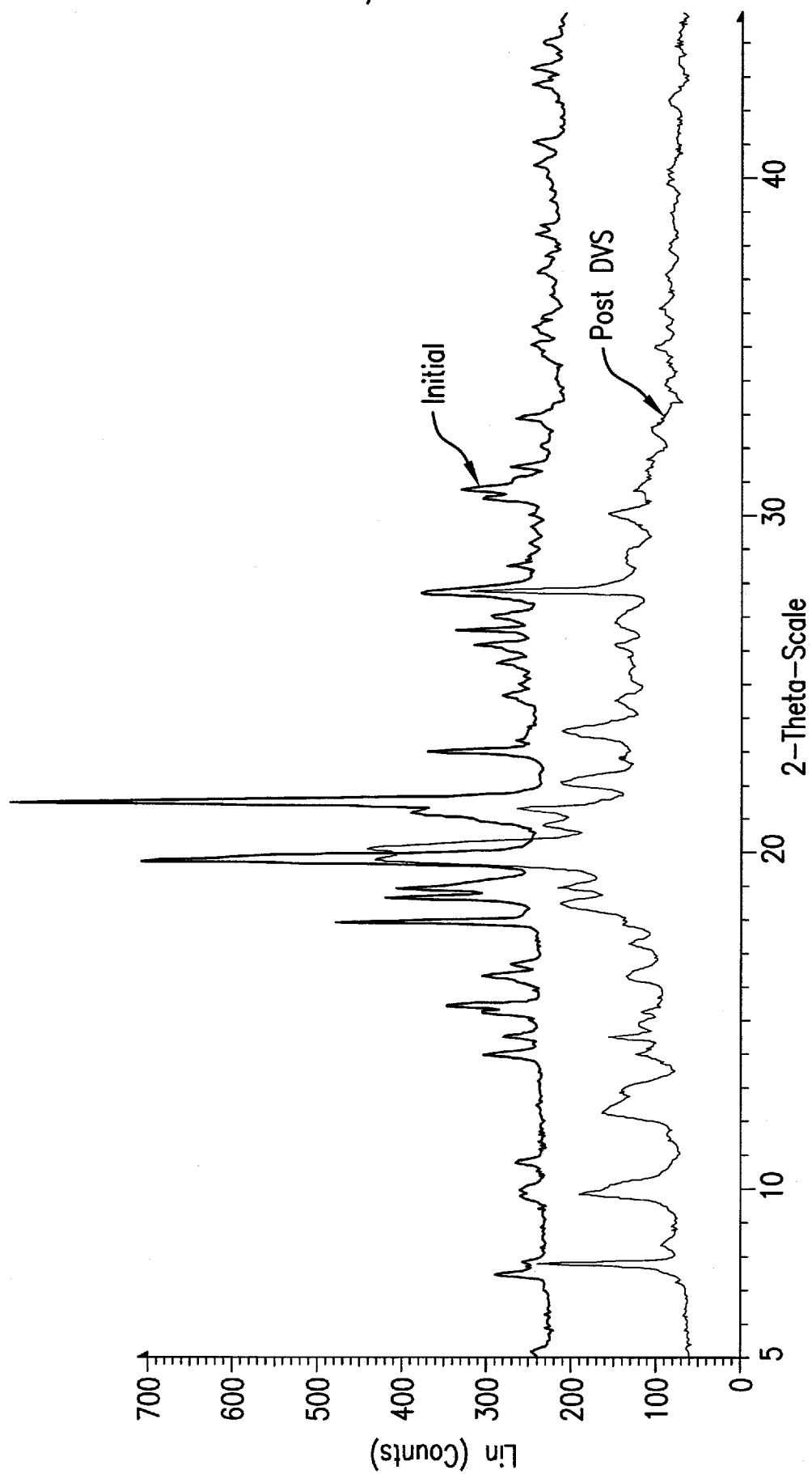


FIG.2

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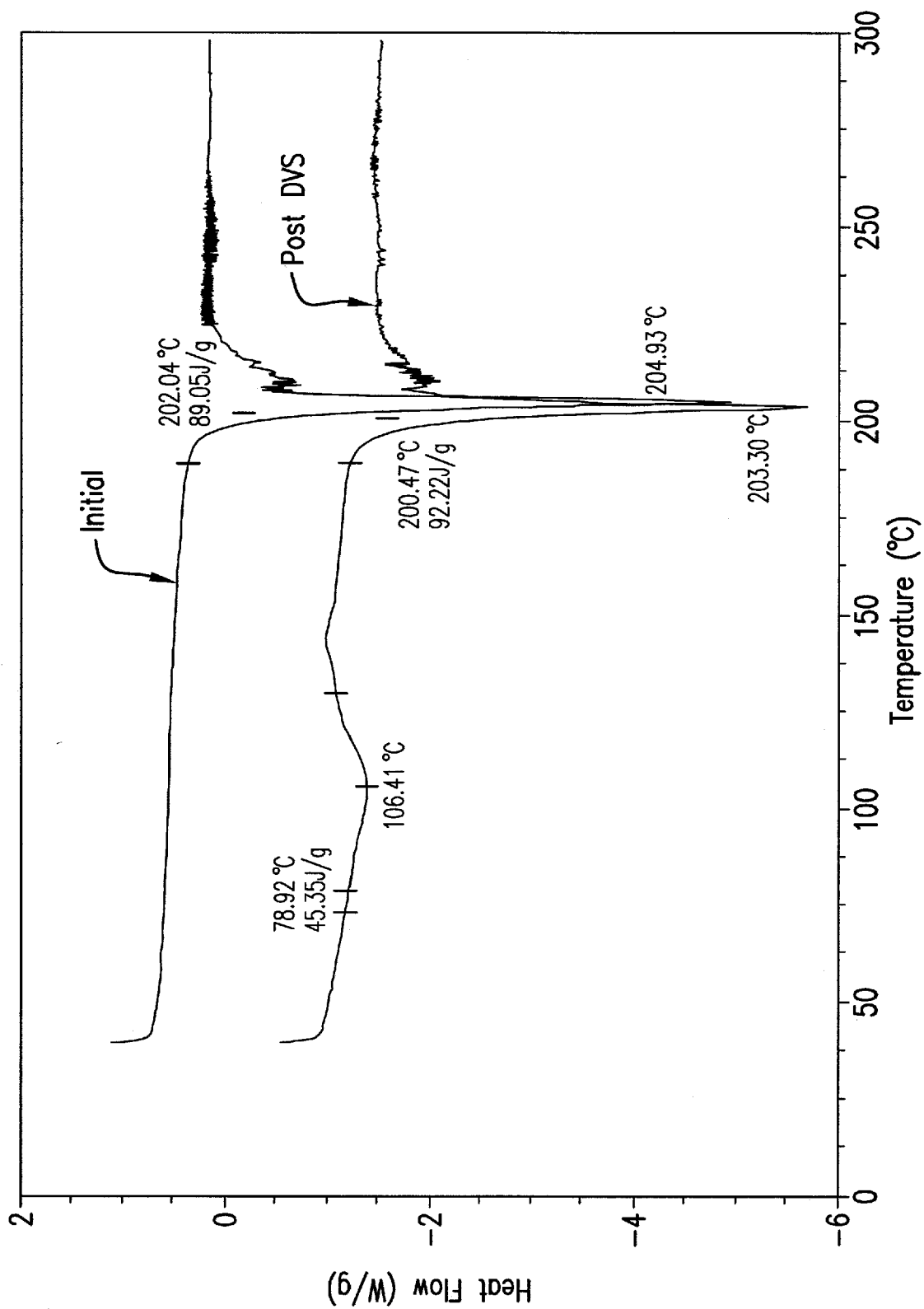


FIG.3

4/6

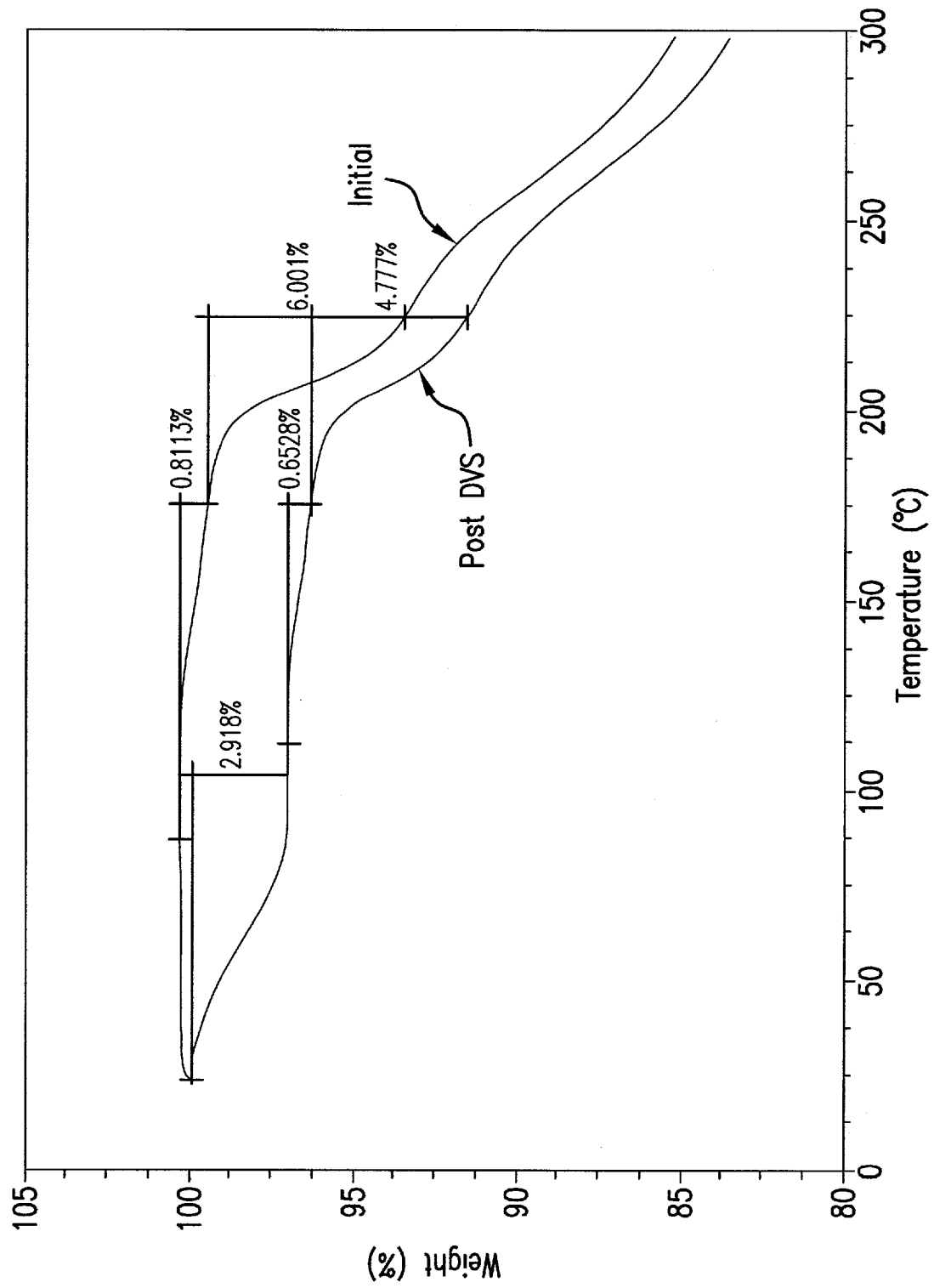


FIG.4

5/6

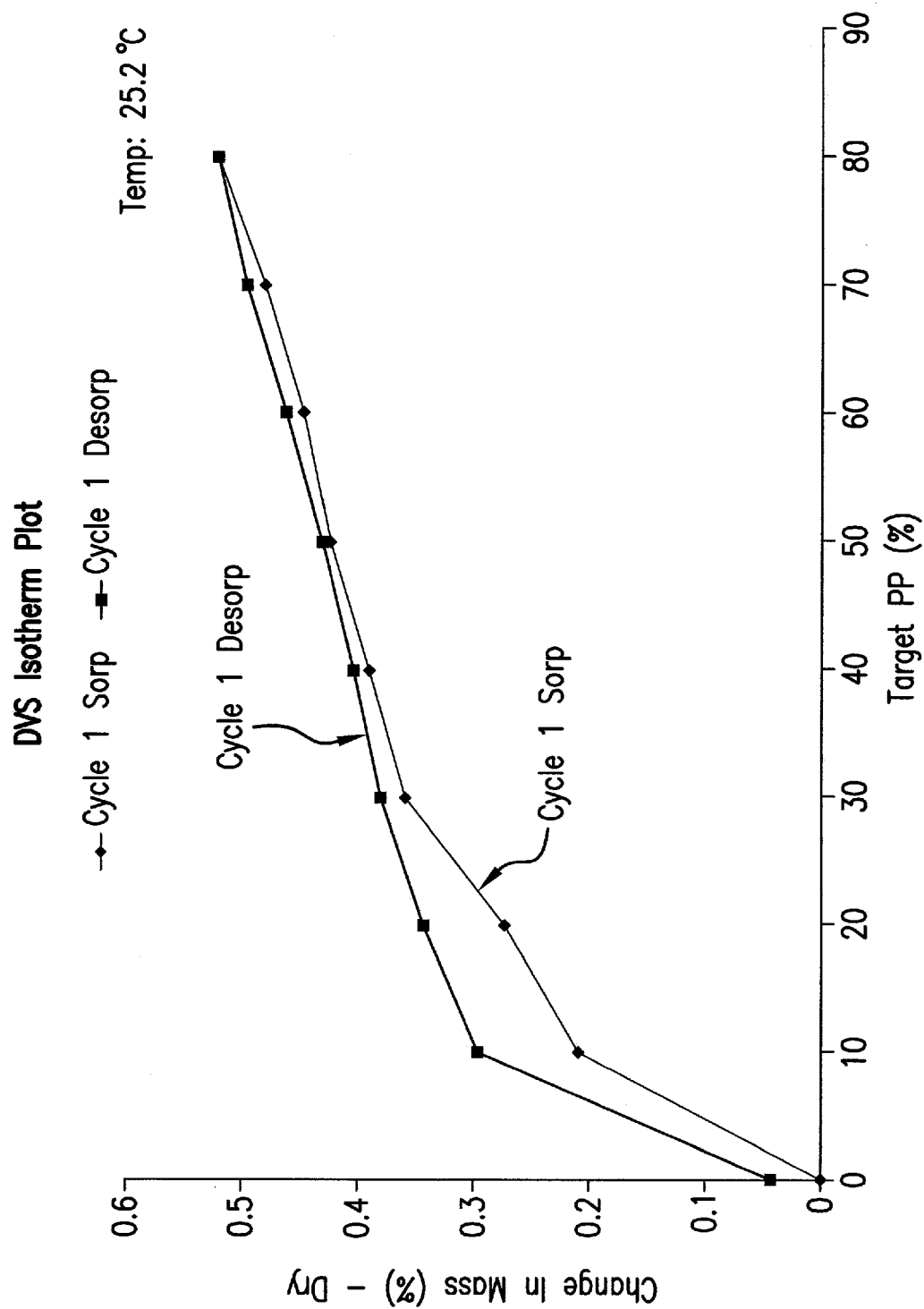


FIG.5

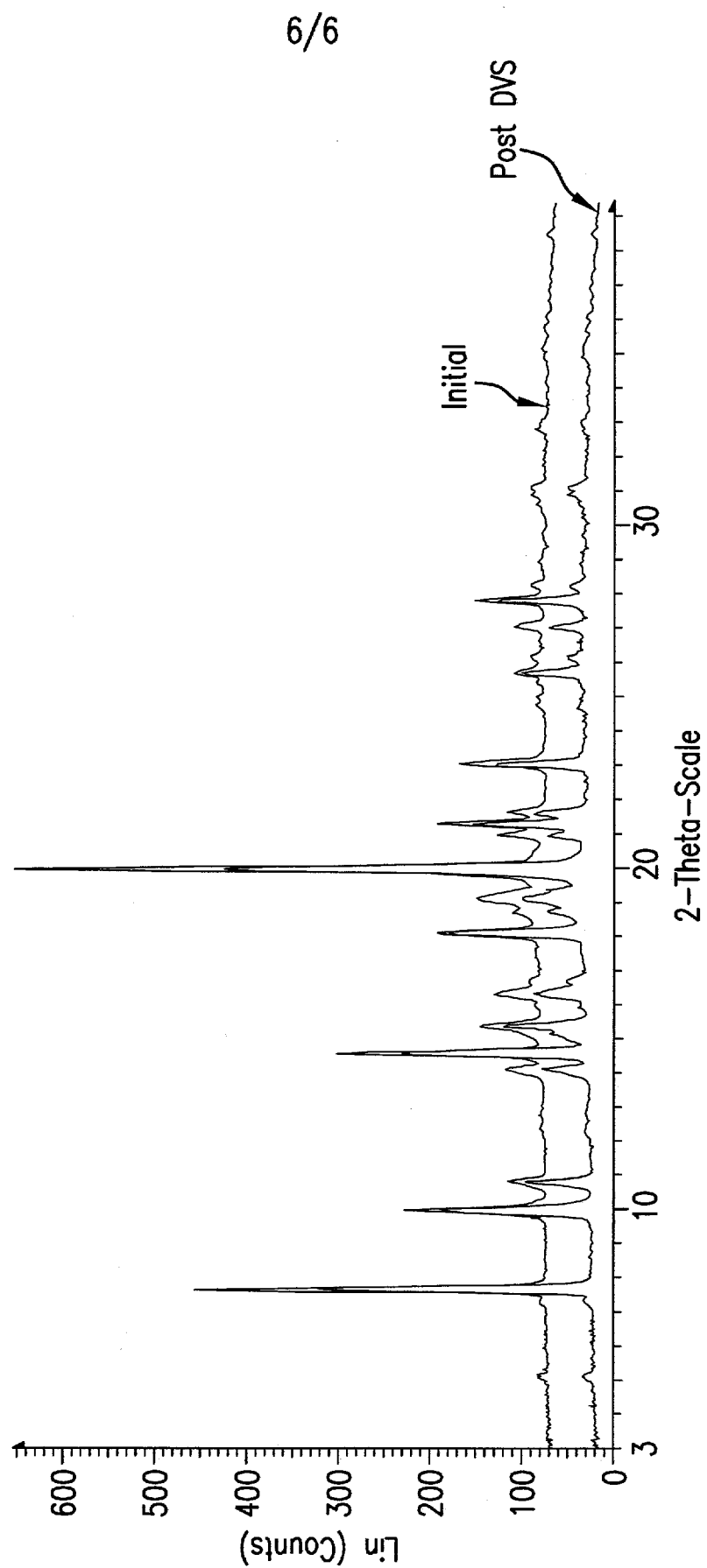


FIG. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/059890

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 A61K31/519 A61P35/00
ADD.

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)
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)

EP0-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/020675 A1 (NOVARTIS AG [CH]; ASTEX THERAPEUTICS LTD [GB]; BESONG GILBERT [GB]; BR) 25 February 2010 (2010-02-25) cited in the application	1-15
Y	page 92; example 74 General procedure F; page 89 - page 91 General procedure A; page 50 - page 51 claim 1	16-18
Y	----- WO 2006/008545 A2 (ASTEX THERAPEUTICS LTD [GB]; BERDINI VALERIO [GB]; EARLY THERESA RACHA) 26 January 2006 (2006-01-26) page 152 - page 153; example 11C ----- -/--	16-18

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

21 March 2012

Date of mailing of the international search report

02/04/2012

Name and mailing address of the ISA/

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

Authorized officer

Bissmire, Stewart

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/059890

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/075783 A2 (WYETH CORP [US]; TSOU HWEI-RU [US]; AYRAL-KALOUSTIAN SEMIRAMIS [US]; B) 5 July 2007 (2007-07-05) Intermediates 13 and 15; page 144 - page 145 -----	16-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/059890

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-11

The succinate salt of
7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide, compositions thereof, their use and processes for its preparation

2. claims: 12-15

processes for the preparation of
2-Chloro-7-cyclopentyl-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (compound of Formula III)

3. claims: 16-18

processes for the preparation of tert-butyl
4-(6-aminopyridin-3-yl)piperazine-1-carboxylate (compound of formula IV)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/059890

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010020675	A1	25-02-2010	AR 073116 A1 13-10-2010
			AU 2009284098 A1 25-02-2010
			CA 2734802 A1 25-02-2010
			CN 102186856 A 14-09-2011
			CO 6341561 A2 21-11-2011
			DO P2011000057 A 31-07-2011
			EA 201100355 A1 31-10-2011
			EC SP11010843 A 31-05-2011
			EP 2331547 A1 15-06-2011
			JP 2012500785 A 12-01-2012
			KR 20110052713 A 18-05-2011
			MA 32555 B1 01-08-2011
			PE 04192011 A1 13-07-2011
			TW 201014858 A 16-04-2010
			US 2010105653 A1 29-04-2010
			US 2011152244 A1 23-06-2011
			UY 32067 A 26-03-2010
			WO 2010020675 A1 25-02-2010

WO 2006008545	A2	26-01-2006	EP 1781647 A2 09-05-2007
			JP 2008506761 A 06-03-2008
			US 2008167309 A1 10-07-2008
			WO 2006008545 A2 26-01-2006

WO 2007075783	A2	05-07-2007	AU 2006331765 A1 05-07-2007
			BR PI0620151 A2 29-06-2010
			CA 2631777 A1 05-07-2007
			CN 101356159 A 28-01-2009
			EP 1963273 A2 03-09-2008
			JP 2009524589 A 02-07-2009
			US 2008085890 A1 10-04-2008
			WO 2007075783 A2 05-07-2007

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 54441 - WO - PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2011/059890	International filing date (<i>day/month/year</i>) 09/11/2011	(Earliest) Priority Date (<i>day/month/year</i>) 10/11/2010
Applicant NOVARTIS AG		

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

This international search report consists of a total of 6 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
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6**bis**(a)).

c. ☐ 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 No. II)

3. ☒ **Unity of invention is lacking** (see Box No 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/US2011/059890

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/059890

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/12 A61K31/519 A61P35/00
ADD.

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)
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)

EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/020675 A1 (NOVARTIS AG [CH]; ASTEX THERAPEUTICS LTD [GB]; BESONG GILBERT [GB]; BR) 25 February 2010 (2010-02-25) cited in the application	1-15
Y	page 92; example 74 General procedure F; page 89 - page 91 General procedure A; page 50 - page 51 claim 1	16-18
Y	----- WO 2006/008545 A2 (ASTEX THERAPEUTICS LTD [GB]; BERDINI VALERIO [GB]; EARLY THERESA RACHA) 26 January 2006 (2006-01-26) page 152 - page 153; example 11C ----- -/-	16-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search

21 March 2012

Date of mailing of the international search report

02/04/2012

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/059890

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/075783 A2 (WYETH CORP [US]; TSOU HWEI-RU [US]; AYRAL-KALOUSTIAN SEMIRAMIS [US]; B) 5 July 2007 (2007-07-05) Intermediates 13 and 15; page 144 - page 145 -----	16-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/059890

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			JP 2009524589 A 02-07-2009
			US 2008085890 A1 10-04-2008
			WO 2007075783 A2 05-07-2007

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-11

The succinate salt of
7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide, compositions thereof, their use and processes for its preparation

2. claims: 12-15

processes for the preparation of
2-Chloro-7-cyclopentyl-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (compound of Formula III)

3. claims: 16-18

processes for the preparation of tert-butyl
4-(6-aminopyridin-3-yl)piperazine-1-carboxylate (compound of formula IV)
