SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-187418- -00000-0000
Fecha: 2013-08-06 16:27:21 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 5

Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIVISIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPUESTOS Y MÉTODOS PARA LA MODULACIÓN DE QUINASAS E INDICACIONES PARA LOS MISMOS

SOLICITANTE: PLEXXIKON, INC.

DIRECCIÓN: 91 Bolívar Drive, Suite A, Berkeley, CA 94710, Estados Undios de América.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 06 de agosto de 2013

P2013/000142

OLARTEMOURE

OLARTE MOURE & ASOCIADOS LTDA.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-187418- -00000-0000
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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 5

PETITORIO - FORMULARIO ÚI
PATENTE PC
ENTRADA EN FASE NACIONAL **P2013/000142**

SOLICITUD DE:

1

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

2

SOLICITANTE (71)

Nombre: PLEXXIKON, INC.

Dirección: 91 Bolívar Drive, Suite A, Berkeley, CA 94710.

Nacionalidad o Domicilio Estados Unidos de América

Lugar de Constitución: Estados Unidos de América

Teléfono: _____ **Fax:** _____

E-mail: _____

IDENTIFICACIÓN

C.C. [ ] **NIT** [ ]

C.E. [ ] **Otro** [ ]

Cual _____

Número _____

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: Carrera 5 No. 34-03 Bogotá D.C.

Teléfono: 601-7700 **Fax:** 601-7799

E-mail: office@olartemoure.com

IDENTIFICACIÓN

C.C. [X] **NIT** [ ]

C.E. [ ] **Otro** [ ]

Cual _____

Número 79782747Bta

TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: VER PAGINA ADJUNTA

5

PCT (86)

Solicitud Internacional No. PCT/US2012/023543 Fecha Febrero 01, 2012

Publicación Internacional No. WO 2012/109075 A1 Fecha Agosto 16, 2012

6

Título (54) **COMPUESTOS Y MÉTODOS PARA LA MODULACIÓN DE QUINASAS E INDICACIONES PARA LOS MISMOS**

Clasificación Internacional (51) A61K 31/407

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Febrero 07, 2011	61/440,339

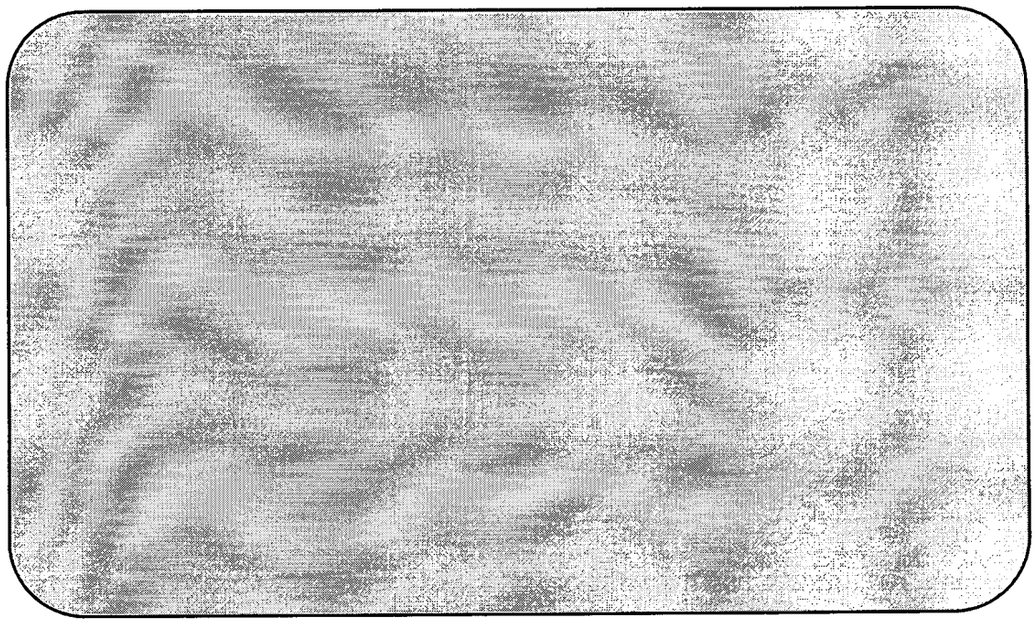
9

Comprobante de pago No. 13- **Fecha** Agosto de 2013

ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple.
- [x] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones bajo la Regla 4.17 del PCT.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] 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.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**



(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

3

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 0075344

Bogotá D.C., Julio 29 de 2013 - 16:26:14

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	532446283	25/07/2013	8.925.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	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
No. 13-187418- -00000-0000
Fecha: 2013-08-06 16:27:21 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 5

IX

LISTA DE INVENTORES

PCT/US2012/023543

Prabha N. IBRAHIM
3380 Lubich Drive,
Mountain View, CA 94040
Estados Unidos de América
Nacionalidad: Estadounidense

Chao ZHANG
397 Springfield Plaza,
Moraga, CA 94556
Estados Unidos de América
Nacionalidad: Estadounidense

Wayne SPEVAK
1585 Campus Drive,
Berkeley, California 94708
Estados Unidos de América
Nacionalidad: Estadounidense

Jiazhong ZHANG
888 Foster City,
CA 94404
Estados Unidos de América
Nacionalidad: China

Guoxian WU
240 Ventura Avenue,
Palo Alto, 94306
Estados Unidos de América
Nacionalidad: Estadounidense

Jack LIN
166 Ferragut Sreet,
Hercules, California 94547
Estados Unidos de América
Nacionalidad: Estadounidense

Hanna CHO
4363 Terrabella Place, Oakland,
California 94619
Estados Unidos de América
Nacionalidad: Estadounidense

Marika NESPI
564 San Luis Road,
Berkeley, CA 94707
Estados Unidos de América
Nacionalidad: Italiana

Songyuan SHI
3979 Vía Cangrejo,
San Diego, California 92130
Estados Unidos de América
Nacionalidad: Estadounidense

Todd EWING
20 Edmund Court,
Walnut Creek, California 94596
Estados Unidos de América
Nacionalidad: Estadounidense

Ying ZHANG
39201 Red Hawk Terrace,
#A204, Fremont, California 94538
Estados Unidos de América
Nacionalidad: China

Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha: 2013 / 08 / 06 (AAAA / MM / DD)	Recorrido:
2020		4

Tipo de Radicación: Entrada: X Salida: ☐ Traslado: ☐ Convenio: ☐

Radicador: | Planilla:

ID	*No. Radicación*	*Consecutivo*	*Item*
1	13-187418	0	7
2			
3			
4			
5			
6			
7			
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9			
10			
11			
12			
13			
14			
15			
16			
17			

Item	*Unidad de Conservación*
1	Bolsa
2	Caja
3	Libro
4	Sobre
5	Tomo
6	**Otro**
Item	***Soporte Documental***
7	CD
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	**Otro**

Observaciones:
ANEXA CD.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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PATENTE DE INVENCIÓN ☐ MODELO DI

- ☐ 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 INVENCIÓN PCT ☑ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada Inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☑ Dibujos de ser estos pertinentes
- ☑ 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 poder otorgado por Plexxikon Inc. a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro, tiene los siguientes textos, firmas y sellos en inglés:

Manuscrito: "Ver reconocimiento adjunto"

Gregory J. Smith
Condado de San Diego
Asesor/Registrador/Registrador del Condado

Oficina del Asesor
1600 Pacific Highway, Room 103
San Diego, CA 92101-2480
Tel. (619) 2363771 - Fax: (619) 557-4056

www.sdarcc.com

Oficina del Registrador del Condado
1600 Pacific Highway, Room 260, PO Box 121750 - San Diego, CA 92112-1750
Tel. (619) 237-0502 - Fax: (619) 557-4155

Yo, Gregory J. Smith, Asesor/Registrador/Registrador del Condado de San Diego, Estado de California, con un sello de Ley, certifico por medio del presente documento que DIANE S. GARCIA, cuyo nombre está suscrito al Juramento o certificado de prueba o reconocimiento del instrumento anexo y por consiguiente escrito, era al momento de tomar dicho juramento, o prueba de reconocimiento, un Notario Público en y para dicho condado, debidamente nombrado y juramentado y debidamente autorizado por las leyes de dicho estado para tomarlos y administrar juramentos y tomar los reconocimientos y pruebas de hechos y otros instrumentos por escrito para ser registrados en este estado. Estoy familiarizado

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

con la escritura de dicho Notario Público y creo que la firma en dicho juramento o certificado de prueba o reconocimiento es genuina. Además certifico que según las leyes del Estado de California, dicho juramento o certificado de prueba o reconocimiento requiere estar sellado, pero la impresión de dicho sello no es exigido por las leyes del Estado de California para ser archivado en mi oficina o en ningún otro lugar.

Fecha: 1º de Junio de 2006.

Firmado en constancia,

(Firmado) Gregory J. Smith, Asesor y Registrador del Condado.

Sello: "Asesor y Registrador del Condado - Condado de San Diego, California".

Oficinas disponibles para servirle:

Chula Vista	El Cajon	Kearny Mesa	San Marcos

Nota: El Modelo de Certificación Notarial lleva la siguiente firma y sello:

Notario Público (Firma): Diane S. Garcia. Notario Publico del Estado de California - Condado de San Diego - Comisión No. 1408800 - Expira el 1º de Abril de 2007.

Sello.

Apostilla adjunta:

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

ESTADO DE CALIFORNIA
Secretario de Estado

APOSTILLA

(Convention du La Haye du 5 octobre 1961)

1. País: ESTADOS UNIDOS DE AMÉRICA

El presente documento público

2. Ha sido firmado por: Gregory J. Smith

3. Actuando en calidad de: Asesor y Registrador del Condado

4. Lleva el sello/estampilla de: Condado de San Diego

Certificado

5. En: San Diego, California

6. El: Día primero de Junio de 2006

7. Por: Sub Secretario de Estado, Estado de California

8. Bajo el No. 137876

9. Sello / estampilla: Gran Sello de Estado de California

10. Firma: BRUCE McPHERSON, Secretario de Estado.
Por: Carolyn J. Johnson

Sello pequeño: "Oficina del Secretario de Estado"

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Poder" Fecha: 5 de Junio de 2006. Traductor: Jorge Enrique Sierra Reyes. Licencia No. 376 de 1993, del Ministerio de Justicia. Dirección: Carrera 15 No. 99-13 Oficina 411. Teléfono: (57-1) 2182308, (57-1) 6232925. Bogotá, Colombia. E-mail: treseser1@yahoo.com. 7431

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

State of California

SECRETARY OF STATE
APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country: United States of America*
   This public document

2. *has been signed by GREGORY J. SMITH*

3. *acting in the capacity of ASSESSOR/RECORDER/COUNTY CLERK*

4. *bears the seal/stamp of the county of SAN DIEGO*
   State of California

CERTIFIED

5. *At SAN DIEGO, California*

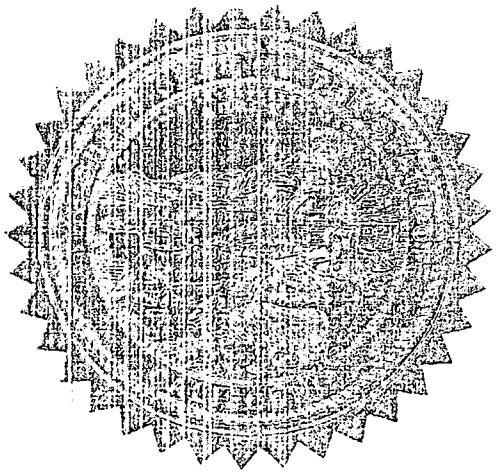
6. *The 1ST day of JUNE, 2006*

7. *by Deputy Secretary of State, State of California*

8. *No. 137876*

9. *Stamp/Seal*

10. *Signature*





Bruce McPherson

Secretary of State

BY Carolyn J. Johnson

Gregory J. Smith

COUNTY OF SAN DIEGO

ASSESSOR / RECORDER / COUNTY CLERK

ASSESSOR'S OFFICE
1600 Pacific Highway, Room 103
San Diego, CA 92101-2480
Tel. (619) 236-3771 • Fax (619) 557-4056

www.sdarcc.com

RECORDER/COUNTY CLERK'S OFFICE
1600 Pacific Highway, Room 260
P.O. Box 121750 • San Diego, CA 92112-1750
Tel. (619) 237-0502 • Fax (619) 557-4155

I, GREGORY J SMITH, Assessor/Recorder/County Clerk of the County of San Diego, State of California, having by law a Seal, DO HEREBY CERTIFY that:

DIANE S GARCIA whose name is subscribed to the oath or Certificate of Proof or Acknowledgement of the annexed instrument and thereon written, was at the time of taking such oath, or Proof or Acknowledgement, a Notary Public, in and for said County, duly commissioned and sworn and duly authorized by the laws of said State to take the same and administer oaths and to take the Acknowledgements and Proofs of Deeds and other instruments in writing to be recorded in this State. I am acquainted with the handwriting of such Notary Public and believe that the signature to said oath or Certificate of Proof Acknowledgement is genuine. I further certify that under the laws of the State of California the said oath or Certificate of Proof or Acknowledgement is required to be under seal, but the impression of said seal is not required by the laws of the State of California to be filed in my office or in any other place.

DATED: June 1, 2006 Witness by hand

GREGORY J SMITH, County Assessor/Recorder/Clerk

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chahín
Zaava Ravid
Jacqueline Chaparro
Jose Luis Londoño
Camilo Alvarez
Felipe Mendoza
Camilo Rodríguez
Santiago Pardo

Of Counsel
Guillermo Chahín
Graciela Melo

Power of Attorney

Poder

The undersigned, domiciled in

El suscrito, PLEXXIKON, INC. domiciliado en 91 Bolivar Drive, Suite A, Berkeley, CA 94710 USA

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.

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: 1/16/06

City,Country/Ciudad,País: Berkeley, CA USA

See attached acknowledgment

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

On this date,
January 16, 2006
The undersigned Notary Public certifies:

1. That

Dean R. Artis

of legal age and domiciled in

91 Bolivar Drive, Berkeley, California 94710 USA

signed the foregoing document.

2. That the grantor has executed the foregoing document as Vice President of Plexxikon, Inc.

3. That Plexxikon, Inc., having its principal place of business located in Berkeley, CA United States 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. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):
Certificate of the President and Secretary of Plexxikon, Inc.

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

Dean R. Artis

mayor de edad y domiciliado

91 Bolivar Drive, Berkeley, California 94710 USA

suscribió el documento que antecede.

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

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

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): Diane S. Garcia
Diane S. Garcia
Notary Public-State of California
San Diego County
Commission No. 1408800
Expires April 1, 2007

DIANE S. GARCIA
Commission # 1408800
Notary Public - California
San Diego County
My Comm. Expires Apr 1, 2007

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS
Traductor: Jorge Enrique Sierra Reyes.

Nota del Traductor:

El Certificado de Presidente y Secretaria de Plexxikon Inc. lleva los siguientes textos, firmas y sellos en inglés:

Gregory J. Smith
Condado de San Diego
Asesor/Registrador/Registrador del Condado

Oficina del Asesor
1600 Pacific Highway, Room 103
San Diego, CA 92101-2480
Tel. (619) 2363771 - Fax: (619) 557-4056

www.sdarcc.com

Oficina del Registrador del Condado
1600 Pacific Highway, Room 260. PO Box: 121750 - San Diego, CA 92112-1750
Tel. (619) 237-0502 - Fax: (619) 557-4155

Yo, Gregory J. Smith, Asesor/Registrador/Registrador del Condado de San Diego, Estado de California, con un sello de Ley, certifico por medio del presente documento que DIANE S. GARCIA, cuyo nombre está suscrito al Juramento o certificado de prueba o reconocimiento del instrumento anexo y por consiguiente escrito, era al momento de tomar dicho juramento, o prueba de reconocimiento, un Notario Público en y para dicho condado, debidamente nombrado y juramentado y debidamente autorizado por las leyes de dicho estado para tomarlos y administrar juramentos y tomar los reconocimientos y pruebas de hechos y otros instrumentos por escrito para ser registrados en este estado. Estoy familiarizado con la escritura de dicho Notario Público y creo que la firma en dicho juramento o certificado de prueba o reconocimiento es genuina. Además certifico que según las leyes del Estado de California, dicho juramento o certificado de prueba o reconocimiento requiere estar sellado, pero la impresión de dicho sello no es

Traductor Oficial
JORGE ENRIQUE SIERRA REYES

exigido por las leyes del Estado de California para ser archivado en mi oficina o en ningún otro lugar.

Fecha: 8 de Mayo de 2006.

Firmado en constancia,

(Firmado) Gregory J. Smith, Asesõr y Registrador del Condado.

Sello: "Asesor y Registrador del Condado - Condado de San Diego, California".

Oficinas disponibles para servirle:

Chula Vista	El Cajon	Kearny Mesa	San Marcos

CERTIFICADO DEL PRESIDENTE Y SECRETARIA DE PLEXXIKON INC.
91 Bolivar Drive
Berkeley, CA 94710

La suscrita, Kathleen Sereda Glaub, certifica lo siguiente:

1. Ella es la Presidente y Secretaria debidamente elegida, calificada y vigente de Plexxikon Inc., una empresa de California (la "Empresa") y está familiarizada con los hechos que se certifican aquí, estando debidamente autorizada para certificarlos y para hacer las declaraciones conforme están certificadas por ella en este documento.
2. Plexxikon Inc. está debidamente constituida, está vigente y el otorgamiento del Poder está dentro del alcance de sus propósitos corporativos y ha sido debidamente autorizado para todas las acciones necesarias por parte de la Empresa.
3. Cada persona mencionada más adelante tiene especificado su puesto al frente, la firma al frente del nombre de dicho funcionario es la firma genuina y tal persona

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1002

está autorizada para ejecutar documentos en nombre de la Empresa; cualquier documento ejecutado por dicha persona entrará en vigencia contra la Empresa.

Nombre	Cargo	Firma
Dean Richard Artis	Vicepresidente, *Lead Generation*	(Firmado)

El suscrito ha ejecutado este certificado como funcionario de la Empresa, este día 2 de mayo de 2006.
(Firmado) Kathleen Sereda Glaub, Presidente y Secretaria.

RECONOCIMIENTO PARA TODOS LOS PROPÓSITOS DE CALIFORNIA

Estado de California, Condado de San Diego
El día 5-2-2006, ante mí, Diane Garcia, Notario, se presentaron personalmente DEAN RICHARD ARTIS/KATHLEEN SEREDA GLAUB, a quienes conozco personalmente como las personas cuyos nombres están suscritos al instrumento adjunto y reconocieron ante mí que ellos lo ejecutaron en sus condiciones autorizadas y que por sus firmas en el instrumento, las personas o la entidad a nombre de la cual ellos actuaron, ejecutaron el instrumento.

En constancia, firmo y sello. (Firmado) Diane S. Garcia - Notario Público.
Sello: Diane S. Garcia - Notario Público de California, Condado de San Diego. Mi comisión #1408800 vence el 1° de Abril de 2007.

Descripción del documento adjunto.
Título o tipo de documento: Certificado
Fecha del documento: 5-2-2006.
No. de páginas: 1
El firmante está representando a PLEXXIKON INC.

Traductor Oficial
JORGE E. [illegible] REYES
Licencia 376 -1993 Minjusticia

Apostilla adjunta:

ESTADO DE CALIFORNIA
Secretario de Estado

APOSTILLA

(Convention du La Haye du 5 octobre 1961)

1. País:	ESTADOS UNIDOS DE AMÉRICA
	El presente documento público
2. Ha sido firmado por:	Gregory J. Smith
3. Actuando en calidad de:	Asesor y Registrador del Condado
4. Lleva el sello/estampilla de:	Condado de San Diego
	Certificado
5. En:	San Diego, California
6. El:	Día 8 de Mayo de 2006
7. Por:	Sub Secretario de Estado, Estado de California
8. Bajo el No.	137384
9. Sello / estampilla:	Gran Sello de Estado de California
10. Firma:	BRUCE McPHERSON, Secretario de Estado.
	Por: (ilegible)
Sello pequeño:	"Oficina del Secretario de Estado"

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Certificado" Fecha: 5 de Junio de 2006. Traductor: Jorge Enrique Sierra Reyes. Licencia No. 376 de 1993, del Ministerio de Justicia. Dirección: Carrera 15 No. 99-13 Oficina 411. Teléfono: (57-1) 2182308, (57-1) 6232925. Bogotá, Colombia. E-mail: treseser1@yahoo.com. 7432

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

State of California

SECRETARY OF STATE
APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country: United States of America*
   This public document

2. *has been signed by GREGORY J. SMITH*

3. *acting in the capacity of COUNTY ASSESSOR/RECORDER/CLERK*

4. *bears the seal/stamp of the county of SAN DIEGO*
   State of California

CERTIFIED

5. *At SAN DIEGO, California*

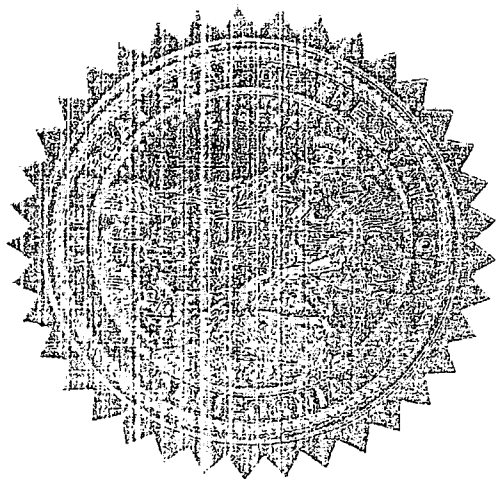
6. *The 8TH day of MAY, 2006*

7. *by Deputy Secretary of State, State of California*

8. *No. 137384*

9. *Stamp/Seal*

10. *Signature*



Bruce McPherson

Secretary of State

BY Cheryl Miller



HI-24 A (REV 4-05)

OSP 05 90772

Gregory J. Smith

COUNTY OF SAN DIEGO

ASSESSOR / RECORDER / COUNTY CLERK

ASSESSOR'S OFFICE
1600 Pacific Highway, Room 103
San Diego, CA 92101-2480
Tel. (619) 236-3771 • Fax (619) 557-4056

www.sdarcc.com

RECORDER/COUNTY CLERK'S OFFICE
1600 Pacific Highway, Room 260
P.O. Box 121750 • San Diego, CA 92112-1750
Tel. (619) 237-0502 • Fax (619) 557-4155

I, GREGORY J SMITH, Assessor/Recorder/County Clerk of the County of San Diego, State of California, having by law a Seal, DO HEREBY CERTIFY that:

DIANE S GARCIA whose name is subscribed to the oath or Certificate of Proof or Acknowledgement of the annexed instrument and thereon written, was at the time of taking such oath, or Proof or Acknowledgement, a Notary Public, in and for said County, duly commissioned and sworn and duly authorized by the laws of said State to take the same and administer oaths and to take the Acknowledgements and Proofs of Deeds and other instruments in writing to be recorded in this State. I am acquainted with the handwriting of such Notary Public and believe that the signature to said oath or Certificate of Proof Acknowledgement is genuine. I further certify that under the laws of the State of California the said oath or Certificate of Proof or Acknowledgement is required to be under seal, but the impression of said seal is not required by the laws of the State of California to be filed in my office or in any other place.

DATED: May 8, 2006 Witness by hand

GREGORY J SMITH, County Assessor/Recorder/Clerk

Branch Offices Available To Serve You

CHULA VISTA
590 Third Avenue
Chula Vista, CA 91910-5617
(619) 498-2200

EL CAJON
200 S. Magnolia Avenue
El Cajon, CA 92020-4524
(619) 401-5700

KEARNY MESA
9225 Clairemont Mesa Blvd.
San Diego, CA 92123-1211
(858) 505-6262

SAN MARCOS
334 Via Vera Cruz, Suite 150
San Marcos, CA 92078-2638
(760) 940-6868

CERTIFICATE OF THE PRESIDENT AND SECRETARY

OF

PLEXXIKON INC.

91 Bolivar Drive
Berkeley, CA 94710

The undersigned, Kathleen Sereda Glaub, hereby certifies as follows:

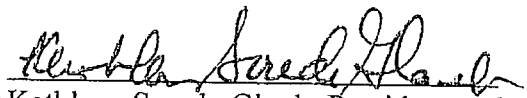
1. She is the duly elected, qualified and acting President and Secretary of Plexxikon Inc. a California corporation (the "***Company***"), and is familiar with the facts herein certified and is duly authorized to certify the same, and to make the statements as certified by her herein.

2. Plexxikon Inc. is duly incorporated, validly existing and the grant of the Power of Attorney is within the scope of its corporate purposes and has been duly authorized by all necessary actions on the part of the Company.

3. Each person named below holds the office set forth opposite such officer's name, the signature opposite such officer's name is such officer's genuine signature and such person is authorized to execute document on behalf of the Company, and any documents executed by such person shall be effective against the Company.

Name	**Title**	**Signature**
Dean Richard Artis	Vice President, Lead Generation	

The undersigned has executed this certificate as an officer of the Company this 2nd day of May, 2006.



Kathleen Sereda Glaub, President and Secretary

CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California
County of SAN DIEGO } ss.

On 5-2-2006 (Date) before me, DIANE GARCIA NOTARY (Name and Title of Officer (e.g., "Jane Doe, Notary Public"))

personally appeared DEAN RICHARD ARMS KATHLEEN SERENA GL[illegible] (Name(s) of Signer(s))

☑ personally known to me
☐ proved to me on the basis of satisfactory evidence

to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

Signature of Notary Public

DIANE S. GARCIA
Commission # 1408800
Notary Public - California
San Diego County
My Comm. Expires Apr 1, 2007

OPTIONAL

Though the information below is not required by law, it may prove valuable to persons relying on the document and could prevent fraudulent removal and reattachment of this form to another document.

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Document Date: 5-2-2006 Number of Pages: 1

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Capacity(ies) Claimed by Signer

Signer's Name: _____

☐ Individual
☐ Corporate Officer — Title(s): _____
☐ Partner — ☐ Limited ☐ General
☐ Attorney-in-Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other: _____

Signer Is Representing: PLEXXIKON INC

RIGHT THUMBPRINT OF SIGNER
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UNITED STATES PATENT AND TRADEMARK OFFICE
UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
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JANUARY 16, 2012

PTAS

STEPHEN E. REITER
P.O. BOX 80278
SAN DIEGO, CA 92138

501785858

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REEL/FRAME: 027529/0599
NUMBER OF PAGES: 11

BRIEF: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

DOCKET NUMBER: 039363-7202

ASSIGNOR:
IBRAHIM, PRABHA N. DOC DATE: 01/11/2012

ASSIGNOR:
ZHANG, CHAO DOC DATE: 01/11/2012

ASSIGNOR:
SPEVAK, WAYNE DOC DATE: 01/11/2012

ASSIGNOR:
ZHANG, JIAZHONG DOC DATE: 01/11/2012

ASSIGNOR:
WU, GUOXIAN DOC DATE: 01/11/2012

ASSIGNOR:
LIN, JACK DOC DATE: 01/11/2012

ASSIGNOR:
CHO, HANNA DOC DATE: 01/12/2012

ASSIGNOR:
NESPI, MARIKA DOC DATE: 01/11/2012

ASSIGNOR:
SHI, SONGYUAN DOC DATE: 01/11/2012

ASSIGNOR:
EWING, TODD DOC DATE: 01/11/2012

ASSIGNOR:
ZHANG, YING DOC DATE: 01/11/2012

ASSIGNEE:
PLEXXIKON INC.
91 BOLIVAR DRIVE, SUITE A
BERKELEY, CALIFORNIA 94710

APPLICATION NUMBER: 61440339 FILING DATE: 02/07/2011
PATENT NUMBER: ISSUE DATE:
TITLE: COMPOUNDS AND METHODS FOR KINASE MODULATION, AND INDICATIONS THEREFOR

ASSIGNMENT RECORDATION BRANCH
PUBLIC RECORDS DIVISION

ASSIGNMENT - WORLDWIDE

For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, each undersigned inventor (hereinafter referred to singly and collectively as "ASSIGNOR") has sold, assigned, and transferred, and by these presents hereby sells, assigns, and transfers, unto

Plexxikon Inc.
91 Bolivar Drive, Suite A
Berkeley, California 94710

(hereinafter referred to as "ASSIGNEE") its successors and assigns, the full and exclusive right, title and interest for the United States, its territories and possessions, and all foreign countries in and to this invention relating to

COMPOUNDS AND METHODS FOR KINASE MODULATION, AND INDICATIONS THEREFOR

as set forth in this United States Patent Application

check one [ ] executed concurrently herewith,
[ ] executed on _____,
[X] Serial No. 61/440,339 Filed: 2/7/2011

as well as in and to (a) all improvements and modifications of the above-identified invention or inventions, (b) the above-identified application and all other applications for Letters Patent of the United States and countries foreign thereto for above-identified invention or inventions and all improvements and modifications thereof, (c) all Letters Patent which may issue from said applications in the United States and countries foreign thereto, (d) all divisions, continuations, reissues, and extensions of said applications and Letters Patent, and (e) the right to claim for any of said applications the full benefits and priority rights under the Patent Cooperation Treaty, the Paris Convention and any other international agreement; such right, title, and interest to be held and enjoyed by ASSIGNEE, its successors and assigns, to the full end of the term or terms for which any and all such Letters Patent may be granted as fully and entirely as would have been held and enjoyed by ASSIGNOR had this Assignment not been made.

ASSIGNOR HEREBY AUTHORIZES ASSIGNEE to file patent applications in any or all countries on the above-identified invention or inventions in the name of the undersigned or in the name of ASSIGNEE or otherwise as ASSIGNEE may deem advisable under the International Convention or otherwise.

ASSIGNOR HEREBY AUTHORIZES AND REQUESTS the Commissioner of Patents and Trademarks to issue said Letters Patent to ASSIGNEE as assignee of the entire interest, for the sole use and benefit of ASSIGNEE, its successors and assigns.

ASSIGNOR HEREBY AGREES (a) to communicate to ASSIGNEE, its successors and assigns, or their representative or agents, all facts and information known or available to ASSIGNOR respecting said invention or inventions, improvements, and modifications including evidence for interference, reexamination, reissue, opposition, revocation, extension, or infringement purposes or other legal, judicial, or administrative proceedings, whenever requested by ASSIGNEE; (b) to testify in person or by affidavit as required by ASSIGNEE, its successors and assigns, in any such proceeding in the United States or a country foreign thereto; (c) to execute and deliver, upon request by ASSIGNEE, all lawful papers including, but not limited to, original, divisional, continuation, and reissue applications, renewals, assignments, powers of attorney, oaths, affidavits, and declarations, depositions; and (d) to provide all reasonable assistance to ASSIGNEE, its successors and assigns, in obtaining and enforcing proper title in and protection for said invention or inventions, improvements, and modifications under the intellectual property laws of the United States and countries foreign thereto.

ASSIGNOR HEREBY REPRESENTS AND WARRANTS that ASSIGNOR has the full and unencumbered right to sell, assign, and transfer the interests sold, assigned, and transferred herein, and that ASSIGNOR has not executed and will not execute any document or instrument in conflict herewith.

ASSIGNOR HEREBY GRANTS to the law firm of **Foley & Lardner LLP** the power and authority to insert in this Assignment any further identification which may be necessary or desirable to comply with the rules of the U.S. Patent and Trademark Office for recordation of this Assignment.

ASSIGNOR UNDERSTANDS AND AGREES that the attorneys and agents of the law firm of **Foley & Lardner LLP** do not personally represent ASSIGNOR OR ASSIGNOR's legal interests, but instead represent the interests of ASSIGNEE; since said attorneys and agents cannot provide legal advice to ASSIGNOR with respect to this Assignment, ASSIGNOR acknowledges its right to seek its own independent legal counsel.

NAME AND SIGNATURE OF INVENTOR

NAME: **PRABHA N. IBRAHIM**

SIGNATURE: _____ DATE: Jan 11th - 2012

NAME AND SIGNATURE OF WITNESSES

NAME: Zhe Wu SIGNATURE: _____ DATE: Jan, 11, 2012

NAME: Jiazhong Zhang SIGNATURE: _____ DATE: 01-11-2012

NAME AND SIGNATURE OF INVENTOR

NAME: **CHAO ZHANG**

SIGNATURE: _____ DATE: Jan 11th - 2012

NAME AND SIGNATURE OF WITNESSES

NAME: Zhe Wu SIGNATURE: _____ DATE: 1/11/2012

NAME: Jiazhong Zhang SIGNATURE: _____ DATE: 01/11/2012

NAME AND SIGNATURE OF INVENTOR

NAME: **WAYNE SPEVAK**

SIGNATURE: _____ DATE: 1/11/12

NAME AND SIGNATURE OF WITNESSES

NAME: Zhe Wu SIGNATURE: _____ DATE: 1/11/2012

NAME: Jiazhong Zhang SIGNATURE: _____ DATE: 01/11/2012

NAME AND SIGNATURE OF INVENTOR

NAME: **JIAZHONG ZHANG**

SIGNATURE: _____ DATE: 01-11-2012

NAME AND SIGNATURE OF WITNESSES

NAME: Zhe Wu SIGNATURE: _____ DATE: 1/11/2012

NAME: SONGYUAN SHI SIGNATURE: _____ DATE: 1/11/2012

NAME AND SIGNATURE OF INVENTOR

NAME: **GUOXIAN WU**

SIGNATURE: _____ DATE: 01-11-2012

NAME AND SIGNATURE OF WITNESSES

NAME: Zhe Wu SIGNATURE: _____ DATE: 1/11/2012

NAME: Jiazhong Zhang SIGNATURE: _____ DATE: 01/11/2012

NAME AND SIGNATURE OF INVENTOR

NAME: **JACK LIN**

SIGNATURE: _____ DATE: 1/11/2012

NAME AND SIGNATURE OF WITNESSES

NAME: Zhe Wu SIGNATURE: _____ DATE: 1/11/2012

NAME: Jiazhong Zhang SIGNATURE: _____ DATE: 01/11/2012

NAME AND SIGNATURE OF INVENTOR

NAME: **HANNA CHO**

SIGNATURE: _____ DATE: 1/12/2012

NAME AND SIGNATURE OF WITNESSES

NAME: HU PAN SIGNATURE: Hu Pan DATE: 1/12/2012

NAME: John Tessman SIGNATURE: _____ DATE: 1/12/2012

NAME AND SIGNATURE OF INVENTOR

NAME: **MARIKA NESPI**

SIGNATURE: _____ DATE: _____

NAME AND SIGNATURE OF WITNESSES

NAME: _____ SIGNATURE: _____ DATE: _____

NAME: _____ SIGNATURE: _____ DATE: _____

NAME AND SIGNATURE OF INVENTOR

NAME: **SONGYUAN SHI**

SIGNATURE: _____ DATE: _____

NAME AND SIGNATURE OF WITNESSES

NAME: _____ SIGNATURE: _____ DATE: _____

NAME: _____ SIGNATURE: _____ DATE: _____

NAME AND SIGNATURE OF INVENTOR

NAME: **HANNA CHO**

SIGNATURE: _____ DATE: _____

NAME AND SIGNATURE OF WITNESSES

NAME: _____ SIGNATURE: _____ DATE: _____

NAME: _____ SIGNATURE: _____ DATE: _____

NAME AND SIGNATURE OF INVENTOR

NAME: **MARIKA NESPI**

SIGNATURE: Marika Nespi DATE: 1/11/2012

NAME AND SIGNATURE OF WITNESSES

NAME: Zhe Wu SIGNATURE: Zhe Wu DATE: 1/11/2012

NAME: Jiazhong Zhang SIGNATURE: Jiazhong Zhang DATE: 01/11/2012

NAME AND SIGNATURE OF INVENTOR

NAME: **SONGYUAN SHI**

SIGNATURE: _____ DATE: 1/9/2012

NAME AND SIGNATURE OF WITNESSES

NAME: Zhe Wu SIGNATURE: Zhe Wu DATE: 1/11/2012

NAME: Jiazhong Zhang SIGNATURE: Jiazhong Zhang DATE: 01/11/2012

NAME AND SIGNATURE OF INVENTOR

NAME: **TODD EWING**

SIGNATURE: _____ DATE: 1/11/2012

NAME AND SIGNATURE OF WITNESSES

NAME: Zhe Wu SIGNATURE: _____ DATE: 1/11/2012

NAME: Jiazhong Zhang SIGNATURE: _____ DATE: 1/11/2012

NAME AND SIGNATURE OF INVENTOR

NAME: **YING ZHANG**

SIGNATURE: _____ DATE: 01/11/2012

NAME AND SIGNATURE OF WITNESSES

NAME: Zhe Wu SIGNATURE: _____ DATE: 1/11/2012

NAME: Jiazhong Zhang SIGNATURE: _____ DATE: 1/11/2012

VIII-3-1	**Declaration: Entitlement to claim priority** Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	In relation to this international application PLEXXIKON, INC. is entitled to claim priority of earlier application No. 61/440,339 by virtue of the following:
VIII-3-1(iv)		an assignment from IBRAHIM, Prabha N. to PLEXXIKON, INC., dated 11 January 2012 (11.01.2012)
VIII-3-1(iv)		an assignment from ZHANG, Chao to PLEXXIKON, INC., dated 11 January 2012 (11.01.2012)
VIII-3-1(iv)		an assignment from SPEVAK, Wayne to PLEXXIKON, INC., dated 11 January 2012 (11.01.2012)
VIII-3-1(iv)		an assignment from ZHANG, Jiazhong to PLEXXIKON, INC., dated 11 January 2012 (11.01.2012)
VIII-3-1(iv)		an assignment from WU, Guoxian to PLEXXIKON, INC., dated 11 January 2012 (11.01.2012)
VIII-3-1(iv)		an assignment from LIN, Jack to PLEXXIKON, INC., dated 11 January 2012 (11.01.2012)
VIII-3-1(iv)		an assignment from CHO, Hanna to PLEXXIKON, INC., dated 11 January 2012 (11.01.2012)
VIII-3-1(iv)		an assignment from NESPI, Marika to PLEXXIKON, INC., dated 11 January 2012 (11.01.2012)
VIII-3-1(iv)		an assignment from SHI, Songyuan to PLEXXIKON, INC., dated 11 January 2012 (11.01.2012)
VIII-3-1(iv)		an assignment from EWING, Todd to PLEXXIKON, INC., dated 11 January 2012 (11.01.2012)
VIII-3-1(iv)		an assignment from ZHANG, Ying to PLEXXIKON, INC., dated 11 January 2012 (11.01.2012)

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 August 2012 (16.08.2012)

WIPO | PCT

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1 February 2012 (01.02.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/440,339 7 February 2011 (07.02.2011) US

(71) Applicant *(for all designated States except US)*: **PLEXXIKON INC.** [US/US]; 91 Bolivar Drive, Suite A, Berkeley, CA 94710 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **IBRAHIM, Prabha N.** [US/US]; 3380 Lubich Drive, Mountain View, CA 94040 (US). **ZHANG, Chao** [US/US]; 397 Springfield Plaza, Moraga, CA 94556 (US). **SPEVAK, Wayne** [US/US]; 1585 Campus Drive, Berkeley, California 94708 (US). **ZHANG, Jiazhong** [CN/US]; 888 Foster City Blvd., Apt. Q4, Foster City, CA 94404 (US). **WU, Guoxian** [US/US]; 240 Ventura Avenue, Palo Alto, CA 94306 (US). **LIN, Jack** [US/US]; 166 Ferragut Street, Hercules, California 94547 (US). **CHO, Hanna** [US/US]; 4363 Terrabella Place, Oakland, California 94619 (US). **NESPI, Marika** [IT/US]; 564 San Luis Road, Berkeley, CA 94707 (US). **SHI, Songyuan** [US/US]; 3979 Via Cangrejo, San Diego, California 92130 (US). **EWING, Todd** [US/US]; 20 Edmund Court, Walnut Creek, California 94596 (US). **ZHANG, Ying** [CN/US]; 39201 Red Hawk Terrace, #A204, Fremont, California 94538 (US).

(74) Agent: **REITER, Stephen E.**; Foley & Lardner LLP, 3579 Valley Centre Drive, Suite 300, San Diego, California 92130 (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 the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

WO 2012/109075 A1

(54) **Title**: COMPOUNDS AND METHODS FOR KINASE MODULATION, AND INDICATIONS THEREFOR

(57) **Abstract**: Compounds active on protein kinases are described, as well as methods of making and using such compounds to treat diseases and conditions associated with aberrant activity of protein kinases.

COMPOUNDS AND METHODS FOR KINASE MODULATION, AND INDICATIONS THEREFOR

FIELD OF THE INVENTION

[0001] The present invention relates to kinases and compounds which selectively modulate kinases, and uses therefor. Particular embodiments contemplate disease indications which are amenable to treatment by modulation of kinase activity by the compounds of the present invention.

BACKGROUND OF THE INVENTION

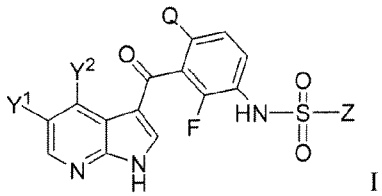
[0002] Receptor protein kinases regulate key signal transduction cascades that control or are involved in the control of a plethora of physiological functions including cellular growth and proliferation, cell differentiation, cellular development, cell division, cell adhesion, stress response, short-range contact-mediated axonal guidance, transcription regulation, aberrant mitogenesis, angiogenesis, abnormal endothelial cell-cell or cell-matrix interactions during vascular development, inflammation, lymphohematopoietic stem cell activity, protective immunity against specific bacteria, allergic asthma, aberrant tissue-specific responses to the activation of the JNK signal transduction pathway, cell transformation, memory, apoptosis, competitive activity-dependent synapse modification at the neuromuscular synapse, immunological mediation of disease, and calcium regulation.

[0003] Specific disease states associated with aberrant regulation of protein kinases include, for example without limitation, acrocephalo-syndactyly type I, acute myeloid leukemia, AIDS-induced non-Hodgkin's lymphoma, Alzheimer's disease, amyotrophic lateral sclerosis, arthritis, asthma, atherosclerosis, atopic dermatitis, autoimmune diseases, bacterial infection, bladder cancer, cancer of the breast, cancer of the central nervous system, cancer of the colon, cancer of the endometrium, cancer of the fallopian tube, cancer of the gastrointestinal tract, cancer of the ovary, heart failure, chronic myeloid leukemia, colon carcinoma, colorectal cancer, chronic obstructive pulmonary disease (COPD), Crouzon Syndrome, diabetes, diabetic nephropathy, emphysema, endometriosis, epidermoid cancer, fibrotic disorders, gastrointestinal stromal tumor (GIST), glomerulonephritis, Graves' disease, head injury, hepatocellular carcinoma, Hirschsprung's disease, human gliomas, immunodeficiency diseases, inflammatory disorders, ischemic stroke, Jackson-Weiss syndrome, leiomyosarcoma, leukemias, lupus nephritis, malignant melanoma, malignant nephrosclerosis, mastocytosis, mast cell tumors, melanoma of the colon, MEN2 syndromes, metabolic disorders, migraine, multiple sclerosis, myeloproliferative disorders, nephritis, neurodegenerative diseases, neurotraumatic diseases, non small cell lung cancer, organ transplant rejection, osteoporosis, pain, Parkinson's disease, Pfeiffer Syndrome, polycystic kidney disease, primary lymphoedema, prostate cancer, psoriasis, vascular restenosis, rheumatoid arthritis, dermal and tissue scarring, selective T-cell defect (STD), severe

combined immunodeficiency (SCID), small cell lung cancer, spinal cord injury, squamous cell carcinoma, systemic lupus erythematosis, testicular cancer, thrombotic microangiopathy syndromes, Wegener's granulomatosis, X-linked agammaglobulinemia, viral infection, diabetic retinopathy, alopecia, erectile dysfunction, macular degeneration, chronic lymphocytic leukemia (CLL), myelodysplastic syndrome (MDS), neurofibromatosis, and tuberous sclerosis. Accordingly, there is a need in the art for compounds and methods of use thereof for the modulation of receptor protein kinases. The present invention meets this and other needs.

SUMMARY OF THE INVENTION

[0004] In one aspect, the present invention provides a compound of formula I:



I

and pharmaceutically acceptable salts, hydrates, solvates, tautomers and isomers thereof; wherein:

Y^1 is selected from the group consisting of CN, halogen, -OH, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{3-6}cycloalkyl, optionally substituted C_{1-6} haloalkyl, optionally substituted C_{1-6} haloalkoxy, optionally substituted aryl and optionally substituted heteroaryl; optionally wherein two adjacent substituents on a substituted aryl or a substituted heteroaryl ring together with the atoms to which they are attached form an optionally substituted 5- or 6-membered ring having from 0 to 3 additional heteroatoms selected from N, O or S;

Y^2 is H, halogen, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, C_{3-8} cycloalkyl-C_{0-4} alkyl or $(R^2)(R^3)$N-, wherein R^2 and R^3 are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, C_{3-8} cycloalkyl-C_{0-4} alkyl, heterocycloalkyl and heterocycloalkyl-C_{1-4} alkyl; or R^2 and R^3 taken together with the nitrogen atom to which they are attached form a three to eight-membered ring having from 0-2 additional heteroatoms as ring members selected from N, O or S; wherein Y^2 is optionally substituted with from one to three groups independently selected from R^e;

Q is selected from H, F, Cl or CH_3;

Z is $-N(R^4)(R^5)$ or $-C(R^6)(R^7)(R^8)$, wherein

R^4 and R^5 are each independently selected from the group consisting of H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{3-8} cycloalkylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl; or R^4 and R^5 taken together

with the nitrogen atom to which they are attached form a four to eight-membered ring having from 0-2 additional heteroatoms as ring members selected from N, O or S, wherein the four to eight-membered ring is optionally substituted;

R^6, R^7 and R^8 are each independently H, optionally substituted C_{1-6} alkyl, optionally substituted, C_{1-6} haloalkyl, optionally substituted C_{1-6} haloalkoxy, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{3-8} cycloalkylalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl or $-X^2R^9$, wherein X^2 is $-NR^{10}$, O or S; R^{10} is H, C_{1-6} alkyl or aryl; and R^9 is H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, wherein R^9 is optionally substituted with from 1 to 3 R^e substituents; or

any two of the R^6, R^7 and R^8 groups taken together with the carbon atom to which they are attached form a 3 to 8-membered optionally substituted non-aromatic ring having from 0 to 2 heteroatoms selected from N, O or S; provided at each occurrence, at least two of the R^6, R^7 and R^8 groups are not simultaneously hydrogen; and with the proviso when (i) Y^1 is halogen, $-CH_3$, -CN, -OMe or 2-methoxypyrimidin-5-yl, Z is other than dimethylamino, diethylamino, 1-pyrrolidine, 1-piperidinyl, 4-morpholinyl, isopropyl, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_3)(CH_2CH_2CH_3)$, cyclobutyl, cyclopentyl or cyclohexyl; and (ii) when Y^1 is 1-methyl-4-pyrazolyl, 3-methylsulfonylphenyl or 3-methylsulfonylaminophenyl, Z is other than cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[0005] In some embodiments,

Y^1 is CN, halogen, -OH, C_{1-6} alkyl, C_{1-6} alkoxy, optionally substituted C_{3-6}cycloalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, aryl and heteroaryl, wherein the aliphatic or aromatic portion of Y^1 is each independently optionally substituted with from 1-5 R^1 substituents;

each R^1 is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-4}-alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4} alkyl or $-R^a$, wherein R^a is selected from halogen, $-CH=CH_2$, -CN, -OH, $-NH_2$, $-NO_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^b$, $-SR^b$, $-OC(O)R^b$, $-OC(S)R^b$, $-C(O)R^b$, $-C(S)R^b$, $-C(O)OR^b$, $-C(S)OR^b$, $-S(O)R^b$, $-S(O)_2R^b$, $-C(O)NHR^b$, $-C(S)NHR^b$, $-C(O)NR^bR^b$, $-C(S)NR^bR^b$, $-S(O)_2NHR^b$, $-S(O)_2NR^bR^b$, $-C(NH)NHR^b$, $-C(NH)NR^bR^b$, $-NHC(O)R^b$, $-NHC(S)R^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NHS(O)_2R^b$, $-NR^bS(O)_2R^b$, $-NHC(O)NHR^b$, $-NHC(S)NHR^b$, $-NR^bC(O)NH_2$, $-NR^bC(S)NH_2$, $-NR^bC(O)NHR^b$, $-NR^bC(S)NHR^b$, $-NHC(O)NR^bR^b$, $-NHC(S)NR^bR^b$, $-NR^bC(O)NR^bR^b$, $-NR^bC(S)NR^bR^b$, $-NHS(O)_2NHR^b$, $-NR^bS(O)_2NH_2$, $-NR^bS(O)_2NHR^b$, $-NHS(O)_2NR^bR^b$, $-NR^bS(O)_2NR^bR^b$, $-NHR^b$ or $-NR^bR^b$,

each R^b is independently selected from the group consisting of C_{1-6} alkyl, halogen, -CN, C_{1-6} alkoxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-4}-alkyl, -OH, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, aryl, aryl-C_{1-4}

alkyl, heteroaryl and heteroarylalkyl; or two R^b substituents when attached to the same nitrogen atom taken together with the nitrogen atom form a three to eight-membered ring having from 0-2 additional heteroatoms as ring members selected from N, O or S; wherein the aliphatic or aromatic portion of R^1 is further optionally substituted with from 1-3 groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl or $-R^e$,

each R^e is independently selected from halogen, -CN, -OH, -CH=CH_2, -NH_2, -NO_2, -C(O)OH, -C(S)OH, -C(O)NH_2, -C(S)NH_2, -S(O)$_2$$NH_2$, -NHC(O)$NH_2$, -NHC(S)$NH_2$, -NHS(O)$_2$$NH_2$, -C(NH)$NH_2$, -$OR^d$, -$SR^d$, -OC(O)$R^d$, -OC(S)$R^d$, -C(O)$R^d$, -C(S)$R^d$, -C(O)$OR^d$, -C(S)$OR^d$, -S(O)$R^d$, -S(O)$_2$$R^d$, -C(O)NH$R^d$, -C(S)NH$R^d$, -C(O)N$R^d$$R^d$, -C(S)N$R^d$$R^d$, -S(O)$_2NHR^d$, -S(O)$_2NR^d$$R^d$, -C(NH)NH$R^d$, -C(NH)N$R^d$$R^d$, -NHC(O)$R^d$, -NHC(S)$R^d$, -N$R^d$C(O)$R^d$, -N$R^d$C(S)$R^d$, -NHS(O)$_2$$R^d$, -N$R^d$S(O)$_2$$R^d$, -NHC(O)NH$R^d$, -NHC(S)NH$R^d$, -N$R^d$C(O)$NH_2$, -N$R^d$C(S)$NH_2$, -N$R^d$C(O)NH$R^d$, -N$R^d$C(S)NH$R^d$, -NHC(O)N$R^d$$R^d$, -NHC(S)N$R^d$$R^d$, -N$R^d$C(O)N$R^d$$R^d$, -N$R^d$C(S)N$R^d$$R^d$, -NHS(O)$_2NHR^d$, -N$R^d$S(O)$_2$$NH_2$, -N$R^d$S(O)$_2NHR^d$, -NHS(O)$_2NR^d$$R^d$, -N$R^d$S(O)$_2NR^d$$R^d$, -NHR^d, R^f or -N$R^d$$R^d$,

each R^d is independently selected from C_{1-6}alkyl, arylalkyl, aryl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl or heterocycloalkylalkyl; and wherein the aromatic portion of R^1 is optionally substituted with from 1-3 substituents independently selected from R^e,

R^e is selected from the group consisting of halogen, -CN, -CH=CH_2, -OH, -NH_2, -NO_2, -C(O)OH, -C(S)OH, -C(O)NH_2, -C(S)NH_2, -S(O)$_2$$NH_2$, -NHC(O)$NH_2$, -NHC(S)$NH_2$, -NHS(O)$_2$$NH_2$, -C(NH)$NH_2$, -$OR^f$, -$SR^f$, -OC(O)$R^f$, -OC(S)$R^f$, -C(O)$R^f$, -C(S)$R^f$, -C(O)$OR^f$, -C(S)$OR^f$, -S(O)$R^f$, -S(O)$_2$$R^f$, -C(O)NH$R^f$, -C(S)NH$R^f$, -C(O)N$R^f$$R^f$, -C(S)N$R^f$$R^f$, -S(O)$_2NHR^f$, -S(O)$_2NR^f$$R^f$, -C(NH)NH$R^f$, -C(NH)N$R^f$$R^f$, -NHC(O)$R^f$, -NHC(S)$R^f$, -N$R^f$C(O)$R^f$, -N$R^f$C(S)$R^f$, -NHS(O)$_2$$R^f$, -N$R^f$S(O)$_2$$R^f$, -NHC(O)NH$R^f$, -NHC(S)NH$R^f$, -N$R^f$C(O)$NH_2$, -N$R^f$C(S)$NH_2$, -N$R^f$C(O)NH$R^f$, -N$R^f$C(S)NH$R^f$, -NHC(O)N$R^f$$R^f$, -NHC(S)N$R^f$$R^f$, -N$R^f$C(O)N$R^f$$R^f$, -N$R^f$C(S)N$R^f$$R^f$, -NHS(O)$_2NHR^f$, -N$R^f$S(O)$_2$$NH_2$, -N$R^f$S(O)$_2NHR^f$, -NHS(O)$_2NR^f$$R^f$, -N$R^f$S(O)$_2NR^f$$R^f$, -NHR^f, -N$R^f$$R^f$ and R^f,

R^f is C_{1-6}alkyl or aryl; or two adjacent R^1 groups on the aryl or heteroaryl ring together with the atoms to which they are attached form a 5- or 6-membered ring having from 0 to 2 additional heteroatoms selected from N, O or S, optionally substituted with from 1 to 3 R^d substituents;

R^4 and R^5 are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl, wherein R^4 or R^5 is optionally substituted with from 1 to 3 members independently selected from C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or R^e; or

R^4 and R^5 taken together with the nitrogen atom to which they are attached form a four to eight membered ring having from 0-2 additional heteroatoms as ring members selected from N, O or S, wherein said four to eight membered ring is optionally substituted with from one to three groups

independently selected from C_{1-6}haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylalkyl, aryl, arylalkyl or R^e; and

R^6, R^7 and R^8 are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkylalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl or $-X^2R^9$; wherein the aliphatic or aromatic portion of R^6, R^7 and R^8 are each optionally substituted with from 1 to 3 members independently selected from the group consisting of C_{3-8} cycloalkyl, C_{3-8} cycloalkylalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl and R^e; or

any two of the R^6, R^7 and R^8 groups taken together with the carbon atom to which they are attached form a 3 to 8-membered carbocyclic ring or a 4 to 8-membered heterocyclic ring having from 1 to 2 heteroatoms as ring members selected from N, O or S, wherein the 3 to 8-membered carbocyclic ring or the 4 to 8-membered heterocyclic ring is optionally substituted with from one to three groups independently selected from C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkyl optionally substituted with R^e, C_{3-8} cycloalkyl, C_{3-8} cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or R^e.

[0006] In another aspect, the invention provides a composition. The composition includes a compound of any of formulas I to In, a compound as recited in any of the claims and described herein or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient or carrier. The invention also provides a composition, which includes a compound as recited in the claims and described herein, a pharmaceutically acceptable excipient or carrier, and another therapeutic agent.

[0007] In yet another aspect, the invention provides a kit, which includes a compound of any of formulas I to In, a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt or solvate thereof. The invention also provides a kit, which includes a composition comprising a compound of formulas I to In, a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt or solvate thereof.

[0008] In another aspect, the invention provides a method for preparing a compound of formula (I) and any of the subgeneric formulas.

[0009] In still another aspect, the invention provides a method for treating a subject suffering from or at risk of a protein kinase mediated diseases or conditions. The method includes administering to the subject an effective amount of a compound of any of formulas I to In, a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt or solvate thereof, or a composition comprising a compound of any of formulas I to In, a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt or solvate thereof.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0010] As used herein the following definitions apply unless clearly indicated otherwise:

[0011] It is noted here that as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

[0012] "Halogen" or "halo" refers to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

[0013] "Hydroxyl" or "hydroxy" refers to the group -OH.

[0014] "Thiol" refers to the group -SH.

[0015] The term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon, having the number of carbon atoms designated (*i.e.* C_{1-6} means one to six carbons). Representative alkyl groups include straight and branched chain alkyl groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. Further representative alkyl groups include straight and branched chain alkyl groups having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. For each of the definitions herein (e.g., alkyl, alkoxy, alkylamino, alkylthio, alkylene, haloalkyl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl), when a prefix is not included to indicate the number of carbon atoms in an alkyl portion, the alkyl moiety or portion thereof will have 12 or fewer main chain carbon atoms or 8 or fewer main chain carbon atoms or 6 or fewer main chain carbon atoms. For example, C_{1-8} alkyl refers to a straight or branched hydrocarbon having 1, 2, 3, 4, 5 or 6 carbon atoms and includes, but are not limited to, C_{1-2} alkyl, C_{1-4} alkyl, C_{2-6} alkyl, C_{2-4} alkyl, C_{1-6} alkyl, C_{2-8} alkyl, C_{1-7} alkyl, C_{2-7} alkyl and C_{3-6} alkyl. "Fluoro substituted alkyl" denotes a alkyl group substituted with one or more fluoro atoms, such as perfluoroalkyl, where preferably the lower alkyl is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. While it is understood that substitutions are attached at any available atom to produce a stable compound, when optionally substituted alkyl is an R group of a moiety such as –OR (e.g. alkoxy), -SR (e.g. thioalkyl), -NHR (e.g. alkylamino), -C(O)NHR, and the like, substitution of the alkyl R group is such that substitution of the alkyl carbon bound to any O, S, or N of the moiety (except where N is a heteroaryl ring atom) excludes substituents that would result in any O, S, or N of the substituent (except where N is a heteroaryl ring atom) being bound to the alkyl carbon bound to any O, S, or N of the moiety.

[0016] The term "alkylene" by itself or as part of another substituent means a linear or branched saturated divalent hydrocarbon moiety derived from an alkane having the number of carbon atoms

indicated in the prefix. For example, (i.e., C_{1-6} means one to six carbons; C_{1-6} alkylene is meant to include methylene, ethylene, propylene, 2-methylpropylene, pentylene, hexylene and the like). C_{1-4} alkylene includes methylene $-CH_2-$, ethylene $-CH_2CH_2-$, propylene $-CH_2CH_2CH_2-$, and isopropylene $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-CH_2-(CH_2)_2CH_2-$, $-CH_2-CH(CH_3)CH_2-$, $-CH_2-C(CH_3)_2-$, $-CH_2-CH_2CH(CH_3)-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer, 8 or fewer, or 6 or fewer carbon atoms being preferred in the present invention. When a prefix is not included to indicate the number of carbon atoms in an alkylene portion, the alkylene moiety or portion thereof will have 12 or fewer main chain carbon atoms or 8 or fewer main chain carbon atoms, 6 or fewer main chain carbon atoms or 4 or fewer main chain carbon atoms.

[0017] The term "alkenylene" refers to a linear bivalent hydrocarbon moiety or a branched monovalent hydrocarbon moiety having the number of carbon atoms indicated in the prefix and containing at least one double bond. For example, i.e., C_{2-6} means two to six carbons; C_{2-6} alkenylene is meant to include, but are not limited to, $-CH=CH-$, $-CH_2-CH=CH-$, $-CH_2-CH=C(CH_3)-$, $-CH=CH-CH=CH-$, and the like). Similarly, the term "alkynylene" refers to a linear bivalent hydrocarbon moiety or a branched monovalent hydrocarbon moiety containing at least one triple bond and having the number of carbon atoms indicated in the prefix. For example, (i.e., C_{2-6} means two to six carbons; C_{2-6} alkynlene is meant to include, but are not limited to, $-C\equiv C-$, $-C\equiv CCH_2-$, $-CH_2-C\equiv CCH_2-$, $-C\equiv CCH(CH_3)-$, and the like. When a prefix is not included to indicate the number of carbon atoms in an alkenylene or alkynlene portion, the alkenylene moiety or portion thereof will have 12 or fewer main chain carbon atoms or 8 or fewer main chain carbon atoms or 6 or fewer main chain carbon atoms, or 4 or fewer main chain carbon atoms.

[0018] "Cycloalkyl" by itself or as part of another substituent, refers to saturated or unsaturated, non-aromatic monocyclic, bicyclic or tricyclic carbon ring systems of 3-10, also 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, adamantyl, and the like. Cycloalkyl refers to hydrocarbon rings having the indicated number of ring atoms (*e.g.*, C_{3-8} cycloalkyl means three to eight ring carbon atoms)

[0019] "Cycloalkylalkyl" refers to an -(alkylene)-cycloalkyl group where alkylene as defined herein has the indicated number of carbon atoms or if unspecified having six or fewer, preferably four or fewer main chain carbon atoms; and cycloalkyl is as defined herein has the indicated number of carbon atoms. C_{3-8}cycloalkylalkyl is meant to have 3 to 8 ring carbon atoms. Exemplary cycloalkylalkyl include, e.g., cyclopropylmethylene, cyclobutylethylene, cyclobutylmethylene, and the like.

[0020] "Haloalkyl," is meant to include alkyl substituted by one to seven halogen atoms. Haloalkyl includes monohaloalkyl and polyhaloalkyl. For example, the term "C_{1-6} haloalkyl" is meant to include trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0021] "Haloalkoxy" refers to a –O-haloalkyl group, where haloalkyl is as defined herein, e. g., trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, and the like.

[0022] "Alkoxy" refers to a –O-alkyl group, where alkyl is as defined herein. "Cycloalkoxy" refers to a –O-cycloalkyl group, where cycloalkyl is as defined herein. "Fluoro substituted alkoxy" denotes alkoxy in which the alkyl is substituted with one or more fluoro atoms, where preferably the alkoxy is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. While it is understood that substitutions on alkoxy are attached at any available atom to produce a stable compound, substitution of alkoxy is such that O, S, or N (except where N is a heteroaryl ring atom), are not bound to the alkyl carbon bound to the alkoxy O. Further, where alkoxy is described as a substituent of another moiety, the alkoxy oxygen is not bound to a carbon atom that is bound to an O, S, or N of the other moiety (except where N is a heteroaryl ring atom), or to an alkene or alkyne carbon of the other moiety.

[0023] "Amino" or "amine" denotes the group $-NH_2$.

[0024] "Alkylamino" refers to a –NH-alkyl group, where alkyl is as defined herein. Exemplary alkylamino groups include CH_3NH-, ethylamino, and the like.

[0025] "Dialkylamino" refers to a –N(alkyl)(alkyl) group, where each alkyl is independently as defined herein. Exemplary dialkylamino groups include dimethylamino, diethylamino, ethylmethylamino, and the like.

[0026] "Cycloalkylamino" denotes the group $-NR^{dd}R^{ee}$, where R^{dd} and R^{ee} combine with the nitrogen to form a 5-7 membered heterocycloalkyl ring, where the heterocycloalkyl may contain an additional heteroatom within the ring, such as O, N, or S, and may also be further substituted with alkyl. Alternatively, "cycloalkylamino" refers to a –NH-cycloalkyl group, where cycloalkyl is as defined herein.

[0027] "Alkylthio" refers to -S-alkyl, where alkyl is as defined herein. Exemplary alkylthio groups include CH_3S-, ethylthio, and the like.

[0028] "Aryl" by itself or as part of another substituent refers to a monocyclic, bicyclic or polycyclic polyunsaturated aromatic hydrocarbon moiety containing 6 to 14 ring carbon atoms. Non-limiting examples of unsubstituted aryl groups include phenyl, 1-naphthyl, 2-naphthyl and 4-biphenyl. Exemplary aryl group, such as phenyl or naphthyl, which may be optionally fused with a cycloalkyl of preferably 5-7, more preferably 5-6, ring members.

[0029] "Arylalkyl" refers to -(alkylene)-aryl, where the alkylene group is as defined herein and has the indicated number of carbon atoms, or if unspecified having six or fewer main chain carbon atoms or four or fewer main chain carbon atoms; and aryl is as defined herein. Examples of arylalkyl include benzyl, phenethyl, and the like.

[0030] "Heteroaryl" by itself or as part of another substituent refers to a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1-4, more preferably 1-3, even more preferably 1-2, heteroatoms independently selected from the group consisting of O, S, and N. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable compound is produced. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrazinyl, indolizinyl, benzo[b]thienyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, pyrazolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazolyl, furanyl, benzofuryl, indolyl, triazinyl, quinoxalinyl, cinnolinyl, phthalaziniyl, benzotriazinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiaxolyl, benzothienyl, quinolyl, isoquinolyl, indazolyl, pteridinyl and thiadiazolyl. "Nitrogen containing heteroaryl" refers to heteroaryl wherein any heteroatoms are N.

[0031] "Heteroarylalkyl" refers to -(alkylene)-heteroaryl, where the alkylene group is as defined herein and has the indicated number of carbon atoms, or if unspecified having six or fewer main chain carbon atoms or four or fewer main chain carbon atoms; and heteroaryl is as defined herein. Examples of heteroarylalkyl include 2-pyridylmethyl, 2-thiazolylethyl, and the like.

[0032] "Heterocycloalkyl" refers to a saturated or unsaturated non-aromatic cycloalkyl group that contains from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized, the remaining ring atoms being C, where one or two C atoms may optionally be replaced by a carbonyl. The heterocycloalkyl may be a monocyclic, a bicyclic or a polycylic ring system of 3 to 12, preferably 4 to 10 ring atoms, more preferably 5 to 8 ring atoms in which one to five ring atoms are heteroatoms selected from –N=, -N-, -O-, -S-, -S(O)-, or $-S(O)_2-$ and further wherein one or two ring atoms are optionally replaced by a -C(O)- group. The heterocycloalkyl can also be a heterocyclic alkyl ring fused with a cycloalkyl, an aryl or a heteroaryl ring. Non limiting examples of heterocycloalkyl groups include pyrrolidinyl, piperidinyl, imidazolidinyl, pyrazolidinyl, butyrolactam moiety, valerolactam moiety, imidazolidinone moiety, hydantoin, dioxolane moiety, phthalimide moiety, piperidine, 1,4-dioxane moiety, morpholinyl, thiomorpholinyl, thiomorpholinyl-S-oxide, thiomorpholinyl-S,S-oxide, piperazinyl, pyranyl, pyridine moiety, 3-pyrrolinyl, thiopyranyl, pyrone moiety, tetrahydrofuranyl, tetrahydrothiophenyl, quinuclidinyl, and the like. A heterocycloalkyl group can be attached to the remainder of the molecule through a ring carbon or a heteroatom.

[0033] "Heterocycloalkylalkyl" refers to -(alkylene)-heterocycloalkyl, where the alkylene group is as defined herein and has the indicated number of carbon atoms, or if unspecified having six or fewer

main chain carbon atoms or four or fewer main chain carbon atoms; and heterocycloalkyl is as defined herein. Examples of heterocycloalkylalkyl include 2-pyridylmethyl, 2-thiazolylethyl, and the like.

[0034] The substituents for alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, alkylene, alkenylene, alkynlene include, but are not limited to, R', halogen, -OH, $-NH_2$, $-NO_2$, -CN, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, -OR', -SR', -OC(O)R', -OC(S)R', -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -S(O)R', $-S(O)_2R'$, -C(O)NHR', -C(S)NHR', -C(O)NR'R", -C(S)NR'R", $-S(O)_2NHR'$, $-S(O)_2NR'R"$, -C(NH)NHR', -C(NH)NR'R", -NHC(O)R', -NHC(S)R', -NR"C(O)R', -NR'C(S)R", $-NHS(O)_2R'$, $-NR'S(O)_2R"$, -NHC(O)NHR', -NHC(S)NHR', $-NR'C(O)NH_2$, $-NR'C(S)NH_2$, -NR'C(O)NHR", -NR'C(S)NHR", -NHC(O)NR'R", -NHC(S)NR'R", -NR'C(O)NR"R"', -NR"'C(S)NR'R", $-NHS(O)_2NHR'$, $-NR'S(O)_2NH_2$, $-NR'S(O)_2NHR"$, $-NHS(O)_2NR'R"$, $-NR'S(O)_2NR"R"'$, -NHR', and -NR'R" in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such group. R', R" and R"' each independently refer to hydrogen, C_{1-8} alkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aryl substituted with 1-3 halogens, C_{1-8} alkoxy, haloalkyl, haloalkoxy or C_{1-8} thioalkoxy groups, or unsubstituted aryl-C_{1-4} alkyl groups. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include 1-pyrrolidinyl and 4-morpholinyl. R', R" and R"' can be further substituted with R^{a1}, halogen, -OH, $-NH_2$, $-NO_2$, -CN, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^{a1}$, $-SR^{a1}$, $-OC(O)R^{a1}$, $-OC(S)R^{a1}$, $-C(O)R^{a1}$, $-C(S)R^{a1}$, $-C(O)OR^{a1}$, $-C(S)OR^{a1}$, $-S(O)R^{a1}$, $-S(O)_2R^{a1}$, $-C(O)NHR^{a1}$, $-C(S)NHR^{a1}$, $-C(O)NR^{a1}R^{a2}$, $-C(S)NR^{a1}R^{a2}$, $-S(O)_2NHR^{a1}$, $-S(O)_2NR^{a1}R^{a2}$, $-C(NH)NHR^{a1}$, $-C(NH)NR^{a1}R^{a2}$, $-NHC(O)R^{a1}$, $-NHC(S)R^{a1}$, $-NR^{a2}C(O)R^{a1}$, $-NR^{a1}C(S)R^{a2}$, $-NHS(O)_2R^{a1}$, $-NR^{a1}S(O)_2R^{a2}$, $-NHC(O)NHR^{a1}$, $-NHC(S)NHR^{a1}$, $-NR^{a1}C(O)NH_2$, $-NR^{a1}C(S)NH_2$, $-NR^{a1}C(O)NHR^{a2}$, $-NR^{a1}C(S)NHR^{a2}$, $-NHC(O)NR^{a1}R^{a2}$, $-NHC(S)NR^{a1}R^{a2}$, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a3}C(S)NR^{a1}R^{a2}$, $-NHS(O)_2NHR^{a1}$, $-NR^{a1}S(O)_2NH_2$, $-NR^{a1}S(O)_2NHR^{a2}$, $-NHS(O)_2NR^{a1}R^{a2}$, $-NR^{a1}S(O)_2NR^{a2}R^{a3}$, $-NHR^{a1}$, and $-NR^{a1}R^{a2}$ in a number ranging from zero to (2n'+1), where n' is the total number of carbon atoms in such group. R^{a1}, R^{a2} and R^{a3} each independently refer to hydrogen, C_{1-8} alkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aryl substituted with 1-3 halogens, C_{1-8} alkoxy, haloalkyl, haloalkoxy or C_{1-8} thioalkoxy groups, or unsubstituted aryl-C_{1-4} alkyl groups. R^{a1}, R^{a2} and R^{a3} can be further substituted with R^{b1}, halogen, -OH, $-NH_2$, $-NO_2$, -CN, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^{b1}$, $-SR^{b1}$, $-OC(O)R^{b1}$, $-OC(S)R^{b1}$, $-C(O)R^{b1}$, $-C(S)R^{b1}$, $-C(O)OR^{b1}$, $-C(S)OR^{b1}$, $-S(O)R^{b1}$, $-S(O)_2R^{b1}$, $-C(O)NHR^{b1}$, $-C(S)NHR^{b1}$, $-C(O)NR^{b1}R^{b2}$, $-C(S)NR^{b1}R^{b2}$, $-S(O)_2NHR^{b1}$, $-S(O)_2NR^{b1}R^{b2}$, $-C(NH)NHR^{b1}$, $-C(NH)NR^{b1}R^{b2}$, $-NHC(O)R^{b1}$, $-NHC(S)R^{b1}$, $-NR^{b2}C(O)R^{b1}$, $-NR^{b1}C(S)R^{b2}$, $-NHS(O)_2R^{b1}$, $-NR^{b1}S(O)_2R^{b2}$, $-NHC(O)NHR^{b1}$, $-NHC(S)NHR^{b1}$, $-NR^{b1}C(O)NH_2$, $-NR^{b1}C(S)NH_2$, $-NR^{b1}C(O)NHR^{b2}$, $-NR^{b1}C(S)NHR^{b2}$, $-NHC(O)NR^{b1}R^{b2}$, $-NHC(S)NR^{b1}R^{b2}$, $-NR^{b1}C(O)NR^{b2}R^{b3}$, $-NR^{b3}C(S)NR^{b1}R^{b2}$,

$-NHS(O)_2NHR^{b1}$, $-NR^{b1}S(O)_2NH_2$, $-NR^{b1}S(O)_2NHR^{b2}$, $-NHS(O)_2NR^{b1}R^{b2}$, $-NR^{b1}S(O)_2NR^{b2}R^{b3}$, $-NHR^{b1}$, and $-NR^{b1}R^{b2}$ in a number ranging from zero to (2p'+1), where p' is the total number of carbon atoms in such group. R^{b1}, R^{b2} and R^{b3} each independently refer to hydrogen, C_{1-8} alkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aryl substituted with 1-3 halogens, C_{1-8} alkoxy, haloalkyl, haloalkoxy or C_{1-8} thioalkoxy groups, or unsubstituted aryl-C_{1-4} alkyl groups.

[0035] Substituents for the aryl and heteroaryl groups are varied and are generally selected from: R', halogen, -OH, $-NH_2$, $-NO_2$, -CN, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, -OR', -SR', -OC(O)R', -OC(S)R', -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -S(O)R', $-S(O)_2R'$, -C(O)NHR', -C(S)NHR', -C(O)NR'R", -C(S)NR'R", $-S(O)_2NHR'$, $-S(O)_2NR'R"$, -C(NH)NHR', -C(NH)NR'R", -NHC(O)R', -NHC(S)R', -NR"C(O)R', -NR'C(S)R", $-NHS(O)_2R'$, $-NR'S(O)_2R"$, -NHC(O)NHR', -NHC(S)NHR', -NR'C(O)NH_2, -NR'C(S)NH_2, -NR'C(O)NHR", -NR'C(S)NHR", -NHC(O)NR'R", -NHC(S)NR'R", -NR'C(O)NR"R"', -NR"'C(S)NR'R", $-NHS(O)_2NHR'$, $-NR'S(O)_2NH_2$, $-NR'S(O)_2NHR"$, $-NHS(O)_2NR'R"$, $-NR'S(O)_2NR"R"'$, -NHR', -NR'R", $-N_3$, perfluoro(C_1-C_4)alkoxy, and perfluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R" and R"' are independently selected from hydrogen, haloalkyl, haloalkoxy, C_{1-8} alkyl, C_{3-6} cycloalkyl, cycloalkylalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryl-C_{1-4} alkyl, and aryloxy-C_{1-4} alkyl. Other suitable substituents include each of the above aryl substituents attached to a ring atom by an alkylene tether of from 1-4 carbon atoms. R', R" and R"' can be further substituted with R^{a1}, halogen, -OH, $-NH_2$, $-NO_2$, -CN, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^{a1}$, $-SR^{a1}$, $-OC(O)R^{a1}$, $-OC(S)R^{a1}$, $-C(O)R^{a1}$, $-C(S)R^{a1}$, $-C(O)OR^{a1}$, $-C(S)OR^{a1}$, $-S(O)R^{a1}$, $-S(O)_2R^{a1}$, $-C(O)NHR^{a1}$, $-C(S)NHR^{a1}$, $-C(O)NR^{a1}R^{a2}$, $-C(S)NR^{a1}R^{a2}$, $-S(O)_2NHR^{a1}$, $-S(O)_2NR^{a1}R^{a2}$, $-C(NH)NHR^{a1}$, $-C(NH)NR^{a1}R^{a2}$, $-NHC(O)R^{a1}$, $-NHC(S)R^{a1}$, $-NR^{a2}C(O)R^{a1}$, $-NR^{a1}C(S)R^{a2}$, $-NHS(O)_2R^{a1}$, $-NR^{a1}S(O)_2R^{a2}$, $-NHC(O)NHR^{a1}$, $-NHC(S)NHR^{a1}$, $-NR^{a1}C(O)NH_2$, $-NR^{a1}C(S)NH_2$, $-NR^{a1}C(O)NHR^{a2}$, $-NR^{a1}C(S)NHR^{a2}$, $-NHC(O)NR^{a1}R^{a2}$, $-NHC(S)NR^{a1}R^{a2}$, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a3}C(S)NR^{a1}R^{a2}$, $-NHS(O)_2NHR^{a1}$, $-NR^{a1}S(O)_2NH_2$, $-NR^{a1}S(O)_2NHR^{a2}$, $-NHS(O)_2NR^{a1}R^{a2}$, $-NR^{a1}S(O)_2NR^{a2}R^{a3}$, $-NHR^{a1}$,$-NR^{a1}R^{a2}$, $-N_3$, perfluoro(C_1-C_4)alkoxy, and perfluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R^{a1}, R^{a2} and R^{a3} are each independently selected from hydrogen, haloalkyl, haloalkoxy, C_{1-8} alkyl, C_{3-6} cycloalkyl, cycloalkylalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryl-C_{1-4} alkyl, or aryloxy-C_{1-4} alkyl. Other suitable substituents include each of the above aryl substituents attached to a ring atom by an alkylene tether of from 1-4 carbon atoms.

[0036] When two substituents are present on adjacent atoms of a substituted aryl or a substituted heteroaryl ring, such substituents may optionally be replaced with a substituent of the formula $-T-C(O)-(CH_2)_q-U-$, wherein T and U are independently -NH-, -O-, $-CH_2-$ or a single bond, and q is an integer of from 0 to 2. Alternatively, when two substituents are present on adjacent atoms of a

substituted aryl or a substituted heteroaryl ring, such substituents may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CH_2-, -O-, -NH-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2NR'$- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, when two substituents are present on adjacent atoms of a substituted aryl or a substituted heteroaryl ring, such substituents may optionally be replaced with a substituent of the formula -$(CH_2)_s$-X-$(CH_2)_t$-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2NR'$-. The substituent R' in -NR'- and -$S(O)_2NR'$- is selected from hydrogen or unsubstituted C_{1-6} alkyl.

[0037] "Protecting group" refers to a grouping of atoms that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity. Examples of protecting groups can be found in T.W. Greene and P.G. Wuts, PROTECTIVE GROUPS IN ORGANIC CHEMISTRY, (Wiley, 4th ed. 2006), Beaucage and Iyer, *Tetrahedron* 48:2223-2311 (1992), and Harrison and Harrison *et al.*, COMPENDIUM OF SYNTHETIC ORGANIC METHODS, Vols. 1-8 (John Wiley and Sons. 1971-1996). Representative amino protecting groups include formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (CBZ), *tert*-butoxycarbonyl (Boc), trimethyl silyl (TMS), 2-trimethylsilyl-ethanesulfonyl (SES), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (FMOC), nitro-veratryloxycarbonyl (NVOC), tri-isopropylsilyl (TIPS), phenylsulphonyl and the like (see also, Boyle, A. L. (Editor), carbamates, amides, N-sulfonyl derivatives, groups of formula -C(O)OR, wherein R is, for example, methyl, ethyl, t-butyl, benzyl, phenylethyl, CH_2=$CHCH_2$-, and the like, groups of the formula -C(O)R', wherein R' is, for example, methyl, phenyl, trifluoromethyl, and the like, groups of the formula -SO_2R", wherein R" is, for example, tolyl, phenyl, trifluoromethyl, 2,2,5,7,8-pentamethylchroman-6-yl, 2,3,6-trimethyl-4-methoxyphenyl, and the like, and silanyl containing groups, such as 2-trimethylsilylethoxymethyl, t-butyldimethylsilyl, triisopropylsilyl, and the like, CURRENT PROTOCOLS IN NUCLEIC ACID CHEMISTRY, John Wiley and Sons, New York,Volume 1, 2000).

[0038] As used herein, the term "composition" refers to a formulation suitable for administration to an intended animal subject for therapeutic purposes that contains at least one pharmaceutically active compound and at least one pharmaceutically acceptable carrier or excipient.

[0039] The term "pharmaceutically acceptable" indicates that the indicated material does not have properties that would cause a reasonably prudent medical practitioner to avoid administration of the material to a patient, taking into consideration the disease or conditions to be treated and the respective route of administration. For example, it is commonly required that such a material be essentially sterile, e.g., for injectibles.

[0040] "Pharmaceutically-acceptable salt" refers to a salt which is acceptable for administration to a patient, such as a mammal (e.g., salts having acceptable mammalian safety for a given dosage

regime). Such salts can be derived from pharmaceutically-acceptable inorganic or organic bases and from pharmaceutically-acceptable inorganic or organic acids, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Salts derived from pharmaceutically- acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary, tertiary and quaternary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N, N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2- dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N- ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Salts derived from pharmaceutically-acceptable acids include acetic, ascorbic, benzenesulfonic, benzoic, camphosulfonic, citric, ethanesulfonic, fumaric, gluconic, glucoronic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, lactobionic, maleic, malic, mandelic, methanesulfonic, mucic, naphthalenesulfonic, nicotinic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic and the like.

[0041] Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S. M. et al, "Pharmaceutical Salts", J. Pharmaceutical Science, 1977, 66:1 -19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0042] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0043] In the present context, the term "therapeutically effective" or "effective amount" indicates that the materials or amount of material is effective to prevent, alleviate, or ameliorate one or more symptoms of a disease or medical condition, and/or to prolong the survival of the subject being treated.

[0044] In the present context, the terms "synergistically effective" or "synergistic effect" indicate that two or more compounds that are therapeutically effective, when used in combination, provide improved therapeutic effects greater than the additive effect that would be expected based on the effect of each compound used by itself.

[0045] By "assaying" is meant the creation of experimental conditions and the gathering of data regarding a particular result of the exposure to specific experimental conditions. For example, enzymes can be assayed based on their ability to act upon a detectable substrate. A compound can be assayed based on its ability to bind to a particular target molecule or molecules.

[0046] As used herein, the terms "ligand" and "modulator" are used equivalently to refer to a compound that changes (i.e., increases or decreases) the activity of a target biomolecule, *e.g.*, an enzyme such as a kinase. Generally a ligand or modulator will be a small molecule, where "small molecule refers to a compound with a molecular weight of 1500 daltons or less, or preferably 1000 daltons or less, 800 daltons or less, or 600 daltons or less. Thus, an "improved ligand" is one that possesses better pharmacological and/or pharmacokinetic properties than a reference compound, where "better" can be defined by one skilled in the relevant art for a particular biological system or therapeutic use.

[0047] The term "binds" in connection with the interaction between a target and a potential binding compound indicates that the potential binding compound associates with the target to a statistically significant degree as compared to association with proteins generally (*i.e.*, non-specific binding). Thus, the term "binding compound" refers to a compound that has a statistically significant association with a target molecule. Preferably a binding compound interacts with a specified target with a dissociation constant (K_D) of 1 mM or less, 1 □M or less, 100 nM or less, 10 nM or less, or 1 nM or less.

[0048] In the context of compounds binding to a target, the terms "greater affinity" and "selective" indicates that the compound binds more tightly than a reference compound, or than the same compound in a reference condition, *i.e.*, with a lower dissociation constant. In some embodiments, the greater affinity is at least 2, 3, 4, 5, 8, 10, 50, 100, 200, 400, 500, 1000, or 10,000-fold greater affinity.

[0049] As used herein in connection with compounds of the invention, the term "synthesizing" and like terms means chemical synthesis from one or more precursor materials. Further, by "assaying" is meant the creation of experimental conditions and the gathering of data regarding a particular result of the experimental conditions. For example, enzymes can be assayed based on their ability to act upon a detectable substrate. A compound or ligand can be assayed based on its ability to bind to a particular target molecule or molecules.

[0050] As used herein, the term "modulating" or "modulate" refers to an effect of altering a biological activity, especially a biological activity associated with a particular biomolecule such as a protein kinase. For example, an agonist or antagonist of a particular biomolecule modulates the activity of that biomolecule, *e.g.*, an enzyme, by either increasing (e.g. agonist, activator), or decreasing (e.g. antagonist, inhibitor) the activity of the biomolecule, such as an enzyme. Such activity is typically indicated in terms of an inhibitory concentration (IC_{50}) or excitation concentration (EC_{50}) of the compound for an inhibitor or activator, respectively, with respect to, for example, an enzyme.

[0051] "Prodrugs" means any compound which releases an active parent drug according to Formula I *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of Formula I are prepared by modifying functional groups present in the compound of Formula I in such a way that the modifications may be cleaved *in vivo* to release the parent compound. Prodrugs may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Prodrugs include compounds of Formula I wherein a hydroxy, amino, carboxyl or sulfhydryl group in a compound of Formula I is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (*e.g.*, acetate, formate, and benzoate derivatives), amides, guanidines, carbamates (*e.g.*, N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds of Formula I, and the like. Preparation, selection, and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series; "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985; and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, each of which are hereby incorporated by reference in their entirety.

[0052] "Tautomer" means compounds produced by the phenomenon wherein a proton of one atom of a molecule shifts to another atom. *See*, Jerry March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structures*, Fourth Edition, John Wiley & Sons, pages 69-74 (1992). The tautomers also refer to one of two or more structural isomers that exist in equilibrium and are readily converted from one isomeric form to another. Examples of include keto-enol tautomers, such as acetone/propen-2-ol, imine-enamine tautomers and the like, ring-chain tautomers, such as glucose/2,3,4,5,6-pentahydroxy-hexanal and the like, the tautomeric forms of heteroaryl groups containing a -N=C(H)-NH- ring atom arrangement, such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles. Where the compound contains, for example, a keto or oxime group or an aromatic moiety, tautomeric isomerism ('tautomerism') can occur. The compounds described herein may have one or more tautomers and therefore include various isomers. A person of ordinary skill in the art would recognize that other tautomeric ring atom arrangements are possible. All such isomeric forms of these compounds are expressly included in the present invention.

[0053] "Isomers" mean compounds having identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". "Stereoisomer" and "stereoisomers" refer to compounds that exist in different stereoisomeric forms if they possess one or more asymmetric centers or a double bond with asymmetric substitution and, therefore, can be produced as individual stereoisomers or as mixtures. Stereoisomers include enantiomers and diastereomers. Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture". Unless otherwise indicated, the description is intended to include individual stereoisomers as well as mixtures. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (*see* discussion in Chapter 4 of ADVANCED ORGANIC CHEMISTRY, 6th edition J. March, John Wiley and Sons, New York, 2007) differ in the chirality of one or more stereocenters.

[0054] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. "Hydrate" refers to a complex formed by combination of water molecules with molecules or ions of the solute. "Solvate" refers to a complex formed by combination of solvent molecules with molecules or ions of the solute. The solvent can be an organic compound, an inorganic compound, or a mixture of both. Solvate is meant to include hydrate. Some examples of solvents include, but are not limited to, methanol, N,N-dimethylformamide, tetrahydrofuran, dimethylsulfoxide, and water. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0055] In the context of the use, testing, or screening of compounds that are or may be modulators, the term "contacting" means that the compound(s) are caused to be in sufficient proximity to a particular molecule, complex, cell, tissue, organism, or other specified material that potential binding interactions and/or chemical reaction between the compound and other specified material can occur.

[0056] As used herein, the term "subject" refers to a living organism that is treated with compounds as described herein, including, but not limted to, any mammal, such as a human, other primates, sports

animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats.

[0057] "Solid form" refers to a solid preparation (i.e. a preparation that is neither gas nor liquid) of a pharmaceutically active compound that is suitable for administration to an intended animal subject for therapeutic purposes. The solid form includes any complex, such as a salt, co-crystal or an amorphous complex, as well as any polymorph of the compound. The solid form may be substantially crystalline, semi-crystalline or substantially amorphous. The solid form may be administered directly or used in the preparation of a suitable composition having improved pharmaceutical properties. For example, the solid form may be used in a formulation comprising at least one pharmaceutically acceptable carrier or excipient.

[0058] "Pain" or a "pain condition" can be acute and/or chronic pain, including, without limitation, arachnoiditis; arthritis (e.g. osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, gout); back pain (e.g. sciatica, ruptured disc, spondylolisthesis, radiculopathy); burn pain; cancer pain; dysmenorrhea; headaches (e.g. migraine, cluster headaches, tension headaches); head and facial pain (e.g. cranial neuralgia, trigeminal neuralgia); hyperalgesia; hyperpathia; inflammatory pain (e.g. pain associated with irritable bowel syndrome, inflammatory bowel disease, ulcerative colitis, Crohn's disease, cystitis, pain from bacterial, fungal or viral infection); keloid or scar tissue formation; labor or delivery pain; muscle pain (e.g. as a result of polymyositis, dermatomyositis, inclusion body myositis, repetitive stress injury (e.g. writer's cramp, carpal tunnel syndrome, tendonitis, tenosynovitis)); myofascial pain syndromes (e.g. fibromyalgia); neuropathic pain (e.g. diabetic neuropathy, causalgia, entrapment neuropathy, brachial plexus avulsion, occipital neuralgia, gout, reflex sympathetic dystrophy syndrome, phantom limb or post-amputation pain, postherpetic neuralgia, central pain syndrome, or nerve pain resulting from trauma (e.g. nerve injury), disease (e.g. diabetes, multiple sclerosis, Guillan-Barre Syndrome, myasthenia gravis, neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, or cancer treatment); pain associated with skin disorders (e.g. shingles, herpes simplex, skin tumors, cysts, neurofibromatosis); sports injuries (e.g. cuts, sprains, strains, bruises, dislocations, fractures, spinal chord, head); spinal stenosis; surgical pain; tactile allodynia; temporomandibular disorders; vascular disease or injury (e.g. vasculitis, coronary artery disease, reperfusion injury (e.g. following ischemia, stroke, or myocardial infarcts)); other specific organ or tissue pain (e.g. ocular pain, corneal pain, bone pain, heart pain, visceral pain (e.g. kidney, gallbladder, gastrointestinal), joint pain, dental pain, pelvic hypersensitivity, pelvic pain, renal colic, urinary incontinence); other disease associated pain (e.g. sickle cell anemia, AIDS, herpes zoster, psoriasis, endometriosis, asthma, chronic obstructive pulmonary disease (COPD), silicosis, pulmonary sarcoidosis, esophagitis, heart burn, gastroesophageal reflux disorder, stomach and duodenal ulcers, functional dyspepsia, bone resorption disease, osteoporosis, cerebral malaria, bacterial meningitis); or pain due to graft v. host rejection or allograft rejections.

[0059] "Unit dosage form" refers to a composition intended for a single administration to treat a subject suffering from a disease or medical condition. Each unit dosage form typically comprises each of the active ingredients of this invention plus pharmaceutically acceptable excipients. Examples of unit dosage forms are individual tablets, individual capsules, bulk powders, liquid solutions, ointments, creams, eye drops, suppositories, emulsions or suspensions. Treatment of the disease or condition may require periodic administration of unit dosage forms, for example: one unit dosage form two or more times a day, one with each meal, one every four hours or other interval, or only one per day. The expression "oral unit dosage form" indicates a unit dosage form designed to be taken orally.

[0060] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

[0061] As used herein in connection with amino acid or nucleic acid sequence, the term "isolate" indicates that the sequence is separated from at least a portion of the amino acid and/or nucleic acid sequences with which it would normally be associated.

[0062] In connection with amino acid or nucleic sequences, the term "purified" indicates that the subject molecule constitutes a significantly greater proportion of the biomolecules in a composition than the proportion observed in a prior composition, e.g., in a cell culture. The greater proportion can be 2-fold, 5-fold, 10-fold, or more than 10-fold, with respect to the proportion found in the prior composition.

[0063] The invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as, but not limited to ^{2}H (deuterium, D), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, and ^{125}I. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition or its isotopes, such as deuterium (D) or tritium (^{3}H). Certain isotopically-labeled compounds of the present invention (e.g., those labeled with .sup.3H and .sup.14C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically

labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Schemes and in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

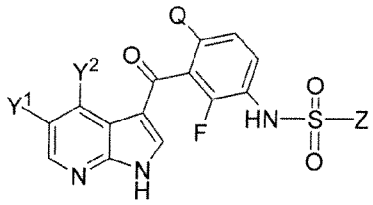
II. General

[0064] The present invention concerns compounds of Formula I and all sub-generic formulae, compounds as recited in the claims, and compounds described herein that are modulators of protein kinases, for example without limitation, the compounds are modulators of at least one of the kinases selected from the group consisting of ABL1, ABL2, ACK, ADRBK1, AKT1, AMPK_A2, A-RAF, ARK5, Aurora_A-C, BMX, CDC42_BPA, CAMK2A, CDK5_p35, CSF1R, DYRK1B, EPHA5, EPHA8, EPHB4, FES, FLT3, FYN, GSK3β, JAK1, KDR, KIT, MAP4K2, MAPK3, MARK2, MARK4, MATK, MET, MINK1, NEK1, NEK2, PAK3, PAK6, PDGFRb, PHKG1, PKC_beta_I, PKC_beta_II, PKC_delta, PKC_gamma, PKC_zeta, SRC, STK24, STK4, ACVR1B_(ALK4), ADRBK2_(GRK3), AKT2_(PKBb), AKT3_(PKBg), ALK, AMPK_A1/B1/G1, ARK5, ASK1, AXL, BRSK1_(SAD1), BrSK2, BTK, CAMK1, CAMK1D, CAMK2A, CAMK2B, CAMK2D, CaMKIdelta, CaMKIIbeta, CaMKIIdelta, CaMKIIgamma, CDC42_BPB, CDK1/CyclinB, CDK2/CyclinA, CDK2/cyclinE, CDK3/cyclinE, CDK5_p25, CDK6/cyclinD3, CDK7/CyclinH/MNAT1, CDK9/CyclinT1, CHEK1, CHEK2, CK1delta, CK1gamma1, CK1gamma2, CK1gamma3, CK2alpha2, CLK1, CLK2, CLK3, CSNK1A1, CSNK1D, CSNK1E, CSNK1G1, CSNK1G2, CSNK1G3, CSNK2A1, CSNK2A2, DAPK1, DAPK2, DAPK3_(ZIPK), DCAMKL2_(DCK2), DDR2, DMPK, DRAK1, DYRK1A, DYRK2, DYRK3, DYRK4, EEF2K, EGFR, EPHA1, EPHA2, EPHA3 EPHA4, EphA7, EPHB1, EPHB2, EPHB3, ERBB2, ERBB4, FER, FGFR1, FGFR2, FGFR3, FGFR4, FLT1, FLT4, FRAP1,GCK, GRK4, GRK5, GRK6, GRK7, GSK3A, GSK3B, Haspin, HCK, Hck activated, HIPK, HIPK2, HIPK3, HIPK4, IGF1R, IGF-1R-activated, IKBKB, IKBKE, IKKalpha, IKKbeta, INSR, INSRR, IR-activated, IRAK1, IRAK4, ITK, JAK2, JAK2_JH1_JH2, JAK3, JNK1alpha1, JNK2alpha2, Lck-activated, LIMK1, LKB1, LOK, LTK, MAP2K1, MAP2K2, MAP2K6, MAP3K8, MAP3K9, MAP4K4, MAPK1, MAPK10, MAPK11, MAPK12, MAPK13, MAPK14, MAPK2, MAPK8, MAPK9, MAPKAPK2, MAPKAPK3, MAPKAPK5, MARK1, MARK3, MELK, MERTK, MKK7beta, MLCK, MRCKalpha, MRCKbeta, MST1R, MST4, mTOR/FKBP12, MUSK, NEK3, NEK4, NEK6, NEK7, NEK9, NLK, NTRK1, NTRK2, NTRK3, PAK2, PAK4, PAK7_(KIAA1264), PAR-1Balpha, PASK, PDGFRalpha, PDGFRbeta, PDK1, PHKG2, PhKgamma2, PIK3CA/PIK3R1, PIK3CG,) PIM1, PIM2, Pim-3, PKBalpha, PKBbeta, PKBgamma, PKCalpha, PKCbetaI, PKCbetaII, PKCdelta, PKCepsilon, PKCeta, PKCgamma, PKCiota, PKCmu, PKCtheta, PKCzeta, PKG1alpha, PKG1beta, PKN1, PLK2, PLK3, PRK2, PRKACA, PRKCA, PRKCE, PRKCH, PRKCI, PRKCN, PRKCQ, PRKD1, PRKD2, PRKG1, PRKG2, PRKX, PTK2, PTK2B, RET, RIPK2, ROCK1, ROCK2, ROS1, RPS6KA1, RPS6KA2, RPS6KA3, RPS6KA4, RPS6KA5, RPS6KA6, RPS6KB1, SGK, SGK2, SGKL, SIK, SNF1LK2, Snk, SRPK1, SRPK2, STK22B, STK22D, STK23, STK25, STK3, STK33,

SYK, TAK1, TAO3, TAOK2, TBK1, Tec activated, TEK, TLK2, Txk, TYK2, TYRO3, ULK2, ULK3, VRK2, WNK2, WNK3, and ZAP70 and the use of such compounds in the treatment of diseases or conditions. In some embodiments, the kinases have less than 20% Inhibition at 1 μM. In other embodiments, the kinases have less than 10% Inhibition at 1 μM.

III. Compounds

[0065] In one aspect, the present invention provides compounds of formula (I):



I

and pharmaceutically acceptable salts, hydrates, solvates, tautomers and isomers thereof; wherein the substituents are as defined in the Summary of the Invention.

[0066] In some embodiments of compounds of formula (I), Y^1 is as defined in the summary of the invention. The All the other substituents of formula (I) are as defined in any of the embodiments described herein. In some preferred embodiments, the compounds have molecular weights less than 600, more preferably, the compounds have molecular weights less than 550. In other preferred embodiments, the compounds have molecular weights less than 500.

[0067] In some embodiments of compounds of formula (I), Y^1 is CN, halogen, -OH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6}cycloalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, aryl or heteroaryl, wherein the aliphatic or aromatic portion of Y^1 is each independently optionally substituted with from 1-5 R^1 substituents; each R^1 is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-4}-alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4} alkyl or $-R^a$, wherein R^a is selected from halogen, $-CH=CH_2$, -CN, -OH, $-NH_2$, $-NO_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^b$, $-SR^b$, $-OC(O)R^b$, $-OC(S)R^b$, $-C(O)R^b$, $-C(S)R^b$, $-C(O)OR^b$, $-C(S)OR^b$, $-S(O)R^b$, $-S(O)_2R^b$, $-C(O)NHR^b$, $-C(S)NHR^b$, $-C(O)NR^bR^b$, $-C(S)NR^bR^b$, $-S(O)_2NHR^b$, $-S(O)_2NR^bR^b$, $-C(NH)NHR^b$, $-C(NH)NR^bR^b$, $-NHC(O)R^b$, $-NHC(S)R^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NHS(O)_2R^b$, $-NR^bS(O)_2R^b$, $-NHC(O)NHR^b$, $-NHC(S)NHR^b$, $-NR^bC(O)NH_2$, $-NR^bC(S)NH_2$, $-NR^bC(O)NHR^b$, $-NR^bC(S)NHR^b$, $-NHC(O)NR^bR^b$, $-NHC(S)NR^bR^b$, $-NR^bC(O)NR^bR^b$, $-NR^bC(S)NR^bR^b$, $-NHS(O)_2NHR^b$, $-NR^bS(O)_2NH_2$, $-NR^bS(O)_2NHR^b$, $-NHS(O)_2NR^bR^b$, $-NR^bS(O)_2NR^bR^b$, $-NHR^b$ or $-NR^bR^b$, wherein each R^b is independently selected from the group consisting of C_{1-6}alkyl, halogen, -CN, C_{1-6}alkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-4}-alkyl, -OH, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, aryl, aryl-C_{1-4}alkyl, heteroaryl and heteroarylalkyl; or two R^b substituents when attached to the same nitrogen atom taken together with the nitrogen atom form a three to eight-

membered ring having from 0-2 additional heteroatoms as ring members selected from N, O or S; wherein the aliphatic or aromatic portion of R^1 is further optionally substituted with from 1-3 groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl or $-R^e$, wherein each R^e is independently selected from halogen, $-CH=CH_2$, -CN, -OH, $-NH_2$, $-NO_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^d$, $-SR^d$, $-OC(O)R^d$, $-OC(S)R^d$, $-C(O)R^d$, $-C(S)R^d$, $-C(O)OR^d$, $-C(S)OR^d$, $-S(O)R^d$, $-S(O)_2R^d$, $-C(O)NHR^d$, $-C(S)NHR^d$, $-C(O)NR^dR^d$, $-C(S)NR^dR^d$, $-S(O)_2NHR^d$, $-S(O)_2NR^dR^d$, $-C(NH)NHR^d$, $-C(NH)NR^dR^d$, $-NHC(O)R^d$, $-NHC(S)R^d$, $-NR^dC(O)R^d$, $-NR^dC(S)R^d$, $-NHS(O)_2R^d$, $-NR^dS(O)_2R^d$, $-NHC(O)NHR^d$, $-NHC(S)NHR^d$, $-NR^dC(O)NH_2$, $-NR^dC(S)NH_2$, $-NR^dC(O)NHR^d$, $-NR^dC(S)NHR^d$, $-NHC(O)NR^dR^d$, $-NHC(S)NR^dR^d$, $-NR^dC(O)NR^dR^d$, $-NR^dC(S)NR^dR^d$, $-NHS(O)_2NHR^d$, $-NR^dS(O)_2NH_2$, $-NR^dS(O)_2NHR^d$, $-NHS(O)_2NR^dR^d$, $-NR^dS(O)_2NR^dR^d$, $-NHR^d$, R^f or $-NR^dR^d$, wherein each R^d is independently selected from C_{1-6} alkyl, arylalkyl, aryl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl or heterocycloalkylalkyl; and wherein the aromatic portion of R^1 is optionally substituted with from 1-3 substituents independently selected from R^e, wherein R^e is selected from the group consisting of halogen, $-CH=CH_2$, -CN, -OH, $-NH_2$, $-NO_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^f$, $-SR^f$, $-OC(O)R^f$, $-OC(S)R^f$, $-C(O)R^f$, $-C(S)R^f$, $-C(O)OR^f$, $-C(S)OR^f$, $-S(O)R^f$, $-S(O)_2R^f$, $-C(O)NHR^f$, $-C(S)NHR^f$, $-C(O)NR^fR^f$, $-C(S)NR^fR^f$, $-S(O)_2NHR^f$, $-S(O)_2NR^fR^f$, $-C(NH)NHR^f$, $-C(NH)NR^fR^f$, $-NHC(O)R^f$, $-NHC(S)R^f$, $-NR^fC(O)R^f$, $-NR^fC(S)R^f$, $-NHS(O)_2R^f$, $-NR^fS(O)_2R^f$, $-NHC(O)NHR^f$, $-NHC(S)NHR^f$, $-NR^fC(O)NH_2$, $-NR^fC(S)NH_2$, $-NR^fC(O)NHR^f$, $-NR^fC(S)NHR^f$, $-NHC(O)NR^fR^f$, $-NHC(S)NR^fR^f$, $-NR^fC(O)NR^fR^f$, $-NR^fC(S)NR^fR^f$, $-NHS(O)_2NHR^f$, $-NR^fS(O)_2NH_2$, $-NR^fS(O)_2NHR^f$, $-NHS(O)_2NR^fR^f$, $-NR^fS(O)_2NR^fR^f$, $-NHR^f$, $-NR^fR^f$ and R^f, wherein R^f is C_{1-6}alkyl or aryl; or two adjacent R^1 groups on the aryl or heteroaryl ring together with the atoms to which they are attached form a 5- or 6-membered ring having from 0 to 2 additional heteroatoms selected from N, O or S, optionally substituted with from 1 to 3 R^d or R^e substituents. In some instances, R^f is C_{1-6}alkyl. In other instances, R^f is aryl, such as phenyl. All the other variables Y^2, Q, Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0068] In some embodiments of compounds of formula (I), Y^1 is aryl or heteroaryl groups, wherein the heteroaryl group has from 1 to 4 heteroatoms as ring members selected from N, O or S; and wherein the aryl or heteroaryl groups are optionally substituted with from 1 to 3 R^1 substituents; or two adjacent R^1 groups on the phenyl or naphthyl ring together with the atoms to which they are attached form a 5- or 6-membered ring having from 0 to 2 additional heteroatoms selected from N, O or S, optionally substituted with from 1 to 3 R^d substituents. In other embodiments, Y^1 is CN, halogen, -OH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6}haloalkyl or C_{1-6}haloalkoxy. In some instances, Y^1 is phenyl, 1-naphthyl or 2-naphthyl, each of which is optionally substituted with from one to three R^1. In other instances, Y^1 is phenyl, 1-naphthyl or 2-naphthyl, each of which is optionally substituted with

from one to three R^a. In other instances, Y^1 is phenyl, 1-naphthyl or 2-naphthyl, each of which is optionally substituted with from one to three R^b. In other instances, Y^1 is phenyl, 1-naphthyl or 2-naphthyl, each of which is optionally substituted with from one to three R^c. In other instances, Y^1 is phenyl, 1-naphthyl or 2-naphthyl, each of which is optionally substituted with from one to three R^d. In other instances, Y^1 is phenyl, 1-naphthyl or 2-naphthyl, each of which is optionally substituted with from one to three R^e. In yet other instances, Y^1 is phenyl, 1-naphthyl or 2-naphthyl, each of which is optionally substituted with from one to three R^a. In some instances, Y^1 is phenyl, 1-naphthyl or 2-naphthyl, is F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl or methylcarbamoyl. All the other variables Y^2, Q, Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0069] In some embodiments of compounds of formula (I), Y^1 is 1H-4-benzotriazolyl, 1H-5-benzotriazolyl, 1H-4-benzimidazolyl, 1H-5-benzimidazolyl, 1H-4-indazolyl, 1H-5-indazolyl, 1H-6-indazolyl, 1H-7-indazolyl, 1H-4-indolyl, 1H-5-indolyl, 1H-6-indolyl, 1H-7-indolyl, 2-oxo-6-indolinyl, 2-oxo-4-indolinyl, 2-oxo-5-indolinyl, 2-oxo-7-indolinyl, 1,2-benzoxazol-4-yl, 1,2-benzoxazol-5-yl, 1,2-benzoxazol-6-yl, 1,2-benzoxazol-7-yl, 1,3-benzoxazol-4-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzoxazol-7-yl, 1,2-benzothiazol-4-yl, 1,2-benzothiazol-5-yl, 1,2-benzothiazol-6-yl, 1,2-benzothiazol-7-yl, 5-quinolinyl, 6-quinolinyl, 7-quinolinyl, 8-quinolinyl, 5-isoquinolinyl, 6-isoquinolinyl, 7-isoquinolinyl, 8-isoquinolinyl, 5-cinnolinyl, 6-cinnolinyl, 7-cinnolinyl, 8-cinnolinyl, 5-quinazolinyl, 6-quinazolinyl, 7-quinazolinyl, 8-quinazolinyl, 5-quinoxalinyl, 6-quinoxalinyl, 7-quinoxalinyl, 8-quinoxalinyl, 4-indanyl, 5-indanyl, 5-tetralinyl, 6-tetralinyl, 1,3-dihydroisobenzofuran-4-yl, 1,3-dihydroisobenzofuran-5-yl, 2,3-dihydrobenzofuran-4-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzofuran-6-yl, 2,3-dihydrobenzofuran-7-yl, 1,3-dihydroisobenzothiophen-4-yl, 1,3-dihydroisobenzothiophen-5-yl, 2,3-dihydrobenzothiophen-4-yl, 2,3-dihydrobenzothiophen-5-yl, 2,3-dihydrobenzothiophen-6-yl, 2,3-dihydrobenzothiophen-7-yl, 4-indolinyl, 5-indolinyl, 6-indolinyl, 7-indolinyl, 5-isochromanyl, 6-isochromanyl, 7-isochromanyl, 8-isochromanyl, 5-chromanyl, 6-chromanyl, 7-chromanyl, 8-chromanyl, 2,3-dihydro-1,3-benzothiazo-4-yl, 2,3-dihydro-1,3-benzothiazo-5-yl, 2,3-dihydro-1,3-benzothiazo-6-yl, 2,3-dihydro-1,3-benzothiazo-7-yl, 2,3-dihydro-1,2-benzothiazo-4-yl, 2,3-dihydro-1,2-benzothiazo-5-yl, 2,3-dihydro-1,2-benzothiazo-6-yl, 2,3-dihydro-1,2-benzothiazo-7-yl, 2,3-dihydro-1,3-benzoxazol-4-yl, 2,3-dihydro-1,3-benzoxazol-5-yl, 2,3-dihydro-1,3-benzoxazol-6-yl, 2,3-dihydro-1,3-benzoxazol-7-yl, 2,3-dihydro-1,2-benzoxazol-4-yl, 2,3-dihydro-1,2-benzoxazol-5-yl, 2,3-dihydro-1,2-benzoxazol-6-yl, 2,3-dihydro-1,2-benzoxazol-7-yl, 4-benzofuranyl, 5-benzofuranyl, 6-benzofuranyl, 7-benzofuranyl, 4-benzothiophenyl, 5-benzothiophenyl, 6-benzothiophenyl or 7-benzothiophenyl, each of which is optionally substituted with from 1 to 3 R^1 substituents; or 1 to 3 R^a substituents; or 1 to 3 R^b

substituents; or 1 to 3 R^c substituents; or 1 to 3 R^d substituents; or 1 to 3 R^e substituents; 1 to 3 R^f substituents; or 1 to 3 substituents selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl or methylcarbamoyl. All the other variables Y^2, Q, Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0070] In some embodiments, Y^1 is 5 or 6-membered heteroaryl, each of which is optionally independently substituted with from 1-3 R^1 groups, wherein the aromatic portion of R^1 is optionally substituted with from 1-3 substituents independently selected from R^e; or two adjacent R^1 groups on the phenyl or naphthyl ring together with the atoms to which they are attached form a 5- or 6-membered ring having from 0 to 2 additional heteroatoms selected from N, O or S, optionally substituted with from 1 to 3 R^d substituents. All the other variables Y^2, Q, Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0071] In some embodiments of compounds of formula (I), Y^1 is 5-pyrimidinyl, 2-pyrimidinyl, 4-pyrimidinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyridazinyl, 3-pyridazinyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrazolyl, 2-pyrazolyl, 3-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-3-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-2-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-4-yl, 1,2,4-triazol-5-yl, 1-oxa-2,3-diazol-4-yl, 1-oxa-2,3-diazol-5-yl, 1-oxa-2,4-diazol-3-yl, 1-oxa-2,4-diazol-5-yl, 1-oxa-2,5-diazol-3-yl, 1-oxa-2,5-diazol-4-yl, 1-thia-2,3-diazol-4-yl, 1-thia-2,3-diazol-5-yl, 1-thia-2,4-diazol-3-yl, 1-thia-2,4-diazol-5-yl, 1-thia-2,5-diazol-3-yl, 1-thia-2,5-diazol-4-yl, 1-tetrazolyl, 3-tetrazolyl, 1H-5-tetrazolyl, 3H-5-tetrazolyl, 2-furanyl, 3-furanyl, 2-thiopenyl or 3-thiophenyl, each of which is optionally substituted with from 1 to 3 R^1 substituents; or 1 to 3 R^a substituents; or 1 to 3 R^b substituents; or 1 to 3 R^c substituents; or 1 to 3 R^d substituents; or 1 to 3 R^e substituents; 1 to 3 R^f substituents; or 1 to 3 substituents selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino, 1-hydroxy-1-methylethyl, methylcarbamoyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl, 1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cycloheyloxy, 4-morpholino, 4-hydroxypiperidinyl,1- piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-t-butoxycarbonylpiperazinyl, azetidinyl, pyrrolidinyl, cyclopropylcarbamoyl, 5-methyl-1,2,4-oxadiazol-3-yl, 5-methyl-1,3,4-oxadiazol-2yl, 5-dimethylamino-1,3,4-oxadiazol-2yl or 5-methylamino-1,3,4-thiadiazol-2-yl. All the

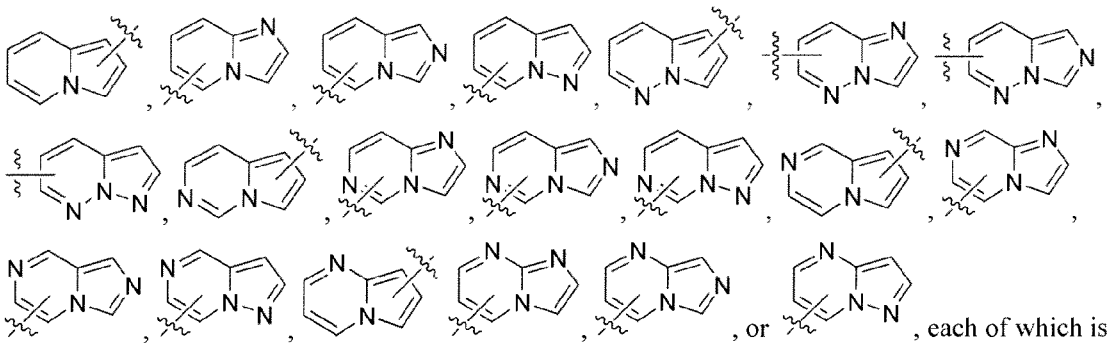
other variables Y^2, Q, Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0072] In certain embodiments of compounds of formula (I), Y^1 is selected from the group consisting of 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-thiophenyl, 3-thiophenyl, 2-amino-quinazolin-5-yl, 2-amino-quinazolin-6-yl, 2-amino-quinazolin-6-yl, 2-amino-quinazolin-7-yl, 2-amino-quinazolin-8-yl, 2-oxo-6-indolinyl, 2-oxo-4-indolinyl, 2-oxo-5-indolinyl, 2-oxo-7-indolinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1H-indazol-4-yl, 1H-indazol-5-yl, 1H-indazol-6-yl and 1H-indazol-7-yl, each of which is substituted with from 1 to 2 susbtituents independently selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, C_2H_5O-, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl, 1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cycloheyloxy, 4-morpholino, 4-hydroxypiperidinyl,1- piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-t-butoxycarbonylpiperazinyl, azetidinyl, pyrrolidinyl, cyclopropylcarbamoyl, 5-methyl-1,2,4-oxadiazol-3-yl, 5-methyl-1,3,4-oxadiazol-2yl, 5-dimethylamino-1,3,4-oxadiazol-2yl, 5-methylamino-1,3,4-thiadiazol-2-yl, methylamino methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl. All the other variables Y^2, Q, Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein

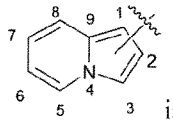
[0073] In other embodiments of compounds of formula (I), Y^1 is 1-benzotriazolyl, 1-benzimidazolyl, 1H-2-benzimidazolyl, 1-indazolyl, 1H-3-indazolyl, 1-indolyl, 1H-2-indolyl, 1H-3-indolyl, 1,2-benzoxazol-3-yl, 1,3-benzoxazol-2-yl, 1,2-benzothiazol-3-yl, 1,3-benzothiazol-2-yl, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 1-isoquinolinyl, 3-isoquinolinyl, 4-isoquinolinyl, 3-cinnolinyl, 4-cinnolinyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinoxalinyl, 2-benzofuranyl, 3-benzofuranyl, 2-benzothiophenyl or 3-benzothiophenyl, each of which is optionally substituted with from 1 to 3 R^1 substituents; or 1 to 3 R^a substituents; or 1 to 3 R^b substituents; or 1 to 3 R^c substituents; or 1 to 3 R^d substituents; or 1 to 3 R^e substituents; 1 to 3 R^f substituents; or 1 to 3 substituents selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino, 1-hydroxy-1-methylethyl, methylcarbamoyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl, 1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cycloheyloxy, 4-morpholino, 4-hydroxypiperidinyl,1- piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-t-butoxycarbonylpiperazinyl, azetidinyl, pyrrolidinyl, cyclopropylcarbamoyl, 5-methyl-1,2,4-oxadiazol-3-yl, 5-methyl-1,3,4-oxadiazol-2yl, 5-dimethylamino-1,3,4-oxadiazol-2yl or 5-methylamino-1,3,4-thiadiazol-2-yl. All the

other variables Y^2, Q, Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

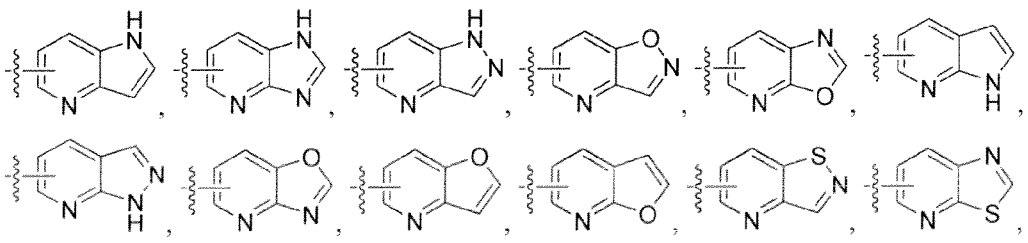
[0074] In some embodiments of compounds of formula (I), Y^1 is selected from:

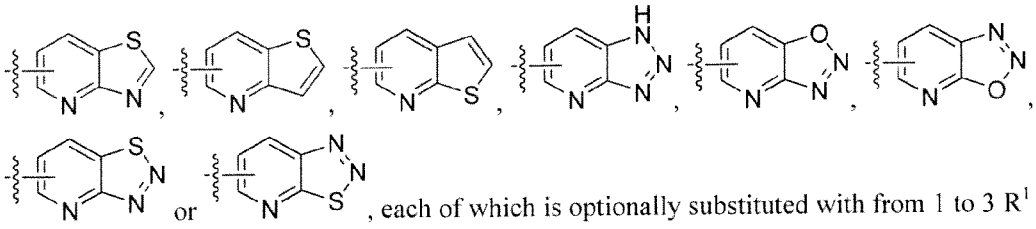
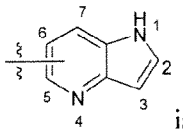


, each of which is optionally substituted with from 1 to 3 R^1 substituents; or 1 to 3 R^a substituents; or 1 to 3 R^b substituents; or 1 to 3 R^c substituents; or 1 to 3 R^d substituents; or 1 to 3 R^e substituents; 1 to 3 R^f substituents; or 1 to 3 substituents selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino, 1-hydroxy-1-methylethyl, methylcarbamoyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl, 1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cycloheyloxy, 4-morpholino, 4-hydroxypiperidinyl,1-piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-t-butoxycarbonylpiperazinyl, azetidinyl, pyrrolidinyl, cyclopropylcarbamoyl, 5-methyl-1,2,4-oxadiazol-3-yl, 5-methyl-1,3,4-oxadiazol-2yl, 5-dimethylamino-1,3,4-oxadiazol-2yl or 5-methylamino-1,3,4-thiadiazol-2-yl, where the wavy line indicate the point of attachment to the rest of the molecule. The notation  means Y^1 can be attached to the rest of the molecule at any of the available positions of the Y^1 group set forth above.

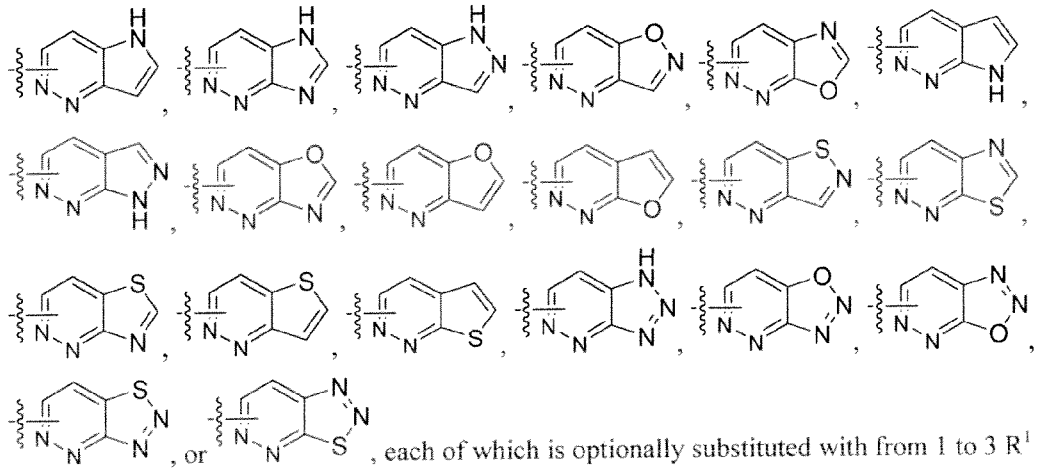
For example,  is meant to include 1-indolizinyl, 2-indolizinyl, 3-indolizinyl, 4-indolizinyl, 5-indolizinyl, 6-indolizinyl, 7-indolizinyl, and 8-indolizinyl (i.e., substitutions can be at 1, 2, 3, 5, 6, 7 or 8 positions of the indolizine ring).

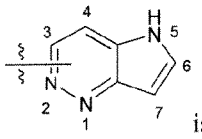
[0075] In some embodiments of compounds of formula (I), Y^1 is selected from:



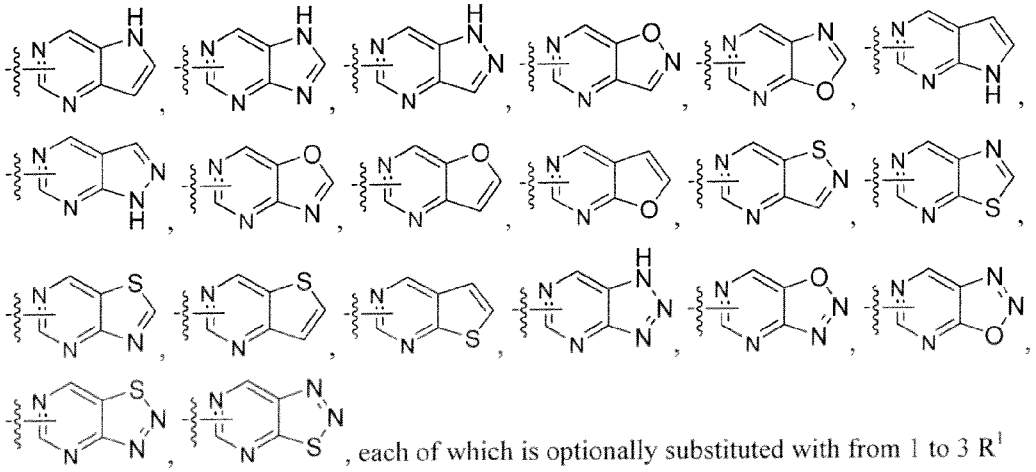

, each of which is optionally substituted with from 1 to 3 R^1 substituents; or 1 to 3 R^a substituents; or 1 to 3 R^b substituents; or 1 to 3 R^c substituents; or 1 to 3 R^d substituents; or 1 to 3 R^e substituents; 1 to 3 R^f substituents; or 1 to 3 substituents selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino, 1-hydroxy-1-methylethyl, methylcarbamoyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl, 1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cycloheyloxy, 4-morpholino, 4-hydroxypiperidinyl,1- piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-t-butoxycarbonylpiperazinyl, azetidinyl, pyrrolidinyl, cyclopropylcarbamoyl, 5-methyl-1,2,4-oxadiazol-3-yl, 5-methyl-1,3,4-oxadiazol-2yl, 5-dimethylamino-1,3,4-oxadiazol-2yl or 5-methylamino-1,3,4-thiadiazol-2-yl, where the wavy line indicates the point of attachment to the rest of the molecule. The notation means Y^1 can be attached to the rest of the molecule at any of the available positions of the Y^1 group set forth above. For example,  is meant to include 1H-pyrrolo[3,2-b]pyridin-1-yl, 1H-pyrrolo[3,2-b]pyridin-2-yl, 1H-pyrrolo[3,2-b]pyridin-3-yl, 1H-pyrrolo[3,2-b]pyridin-5-yl, 1H-pyrrolo[3,2-b]pyridin-6-yl and 1H-pyrrolo[3,2-b]pyridin-7-yl (i.e., substitutions can be at 1, 2, 3, 5, 6, or 7 positions of the pyrrolo[3,2-b]pyridine ring). All the other variables Y^2, Q, Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0076] In some embodiments of compounds of formula (I), Y^1 is selected from:

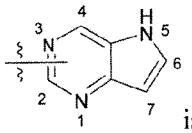

, each of which is optionally substituted with from 1 to 3 R^1

substituents; or 1 to 3 R^a substituents; or 1 to 3 R^b substituents; or 1 to 3 R^c substituents; or 1 to 3 R^d substituents; or 1 to 3 R^e substituents; 1 to 3 R^f substituents; or 1 to 3 substituents selected from F, Cl, Br, I, -CN, -OH, -CF_3, NH_2, CF_3O-, CH_3-, CH_3O, -NO_2, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino, 1-hydroxy-1-methylethyl, methylcarbamoyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl, 1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cycloheyloxy, 4-morpholino, 4-hydroxypiperidinyl,1- piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-t-butoxycarbonylpiperazinyl, azetidinyl, pyrrolidinyl, cyclopropylcarbamoyl, 5-methyl-1,2,4-oxadiazol-3-yl, 5-methyl-1,3,4-oxadiazol-2yl, 5-dimethylamino-1,3,4-oxadiazol-2yl or 5-methylamino-1,3,4-thiadiazol-2-yl, where the wavy line indicates the point of attachment to the rest of the molecule. The notation  means Y^1 can be attached to the rest of the molecule at any of the available positions of the Y^1 group set forth above. For example,  is meant to include 5H-pyrrolo[3,2-c]pyridazin-3-yl, 5H-pyrrolo[3,2-c]pyridazin-4-yl, 5H-pyrrolo[3,2-c]pyridazin-5-yl, 5H-pyrrolo[3,2-c]pyridazin-6-yl, 5H-pyrrolo[3,2-c]pyridazin-7-yl (i.e., substitutions can be at 3, 4, 5, 6, or 7 positions of the 5H-pyrrolo[3,2-c]pyridazine ring). All the other variables Y^2, Q, Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

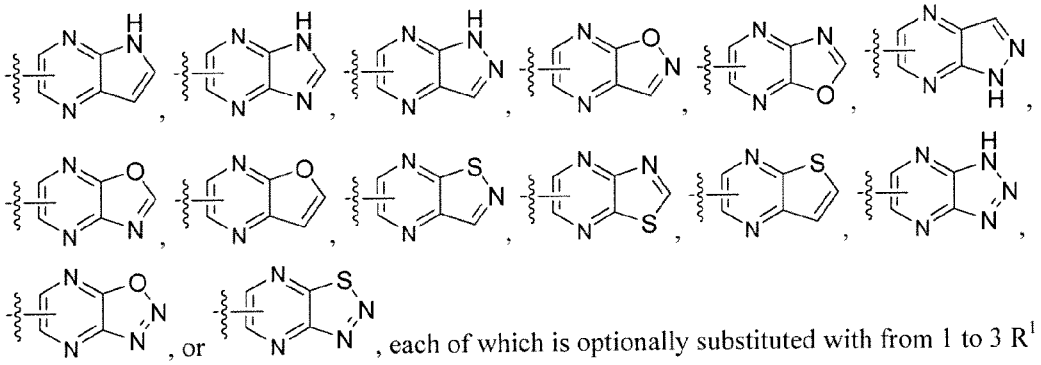
[0077] In some embodiments of compounds of formula (I), Y^1 is selected from:



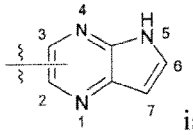
, each of which is optionally substituted with from 1 to 3 R^1 substituents; or 1 to 3 R^a substituents; or 1 to 3 R^b substituents; or 1 to 3 R^c substituents; or 1 to 3 R^d substituents; or 1 to 3 R^e substituents; 1 to 3 R^f substituents; or 1 to 3 substituents selected from F, Cl, Br, I, -CN, -OH, -CF_3, NH_2, CF_3O-, CH_3-, CH_3O, -NO_2, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-

cyclopropylethylamino, 2-cyclopropylethylamino, 1-hydroxy-1-methylethyl, methylcarbamoyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl, 1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cycloheyloxy, 4-morpholino, 4-hydroxypiperidinyl,1- piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-t-butoxycarbonylpiperazinyl, azetidinyl, pyrrolidinyl, cyclopropylcarbamoyl, 5-methyl-1,2,4-oxadiazol-3-yl, 5-methyl-1,3,4-oxadiazol-2yl, 5-dimethylamino-1,3,4-oxadiazol-2yl or 5-methylamino-1,3,4-thiadiazol-2-yl, where the wavy line indicates the point of attachment to the rest of the molecule. The notation  means Y^1 can be attached to the rest of the molecule at any of the available positions of the Y^1 group set forth above. For example,  is meant to include 5H-pyrrolo[3,2-c]pyrimidin-2-yl, 5H-pyrrolo[3,2-c]pyrimidin-4-yl, 5H-pyrrolo[3,2-c]pyrimidin-5-yl, 5H-pyrrolo[3,2-c]pyrimidin-6-yl and 5H-pyrrolo[3,2-c]pyrimidin-7-yl (i.e., substitutions can be at 2, 4, 5, 6, or 7 positions of the 5H-pyrrolo[3,2-c]pyrimidine ring). All the other variables Y^2, Q, Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0078] In some embodiments of compounds of formula (I), Y^1 is selected from:



each of which is optionally substituted with from 1 to 3 R^1 substituents; or 1 to 3 R^a substituents; or 1 to 3 R^b substituents; or 1 to 3 R^c substituents; or 1 to 3 R^d substituents; or 1 to 3 R^e substituents; 1 to 3 R^f substituents; or 1 to 3 substituents selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino, 1-hydroxy-1-methylethyl, methylcarbamoyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl, 1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cycloheyloxy, 4-morpholino, 4-hydroxypiperidinyl,1- piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-t-butoxycarbonylpiperazinyl, azetidinyl, pyrrolidinyl, cyclopropylcarbamoyl, 5-methyl-1,2,4-oxadiazol-3-yl, 5-methyl-1,3,4-oxadiazol-2yl, 5-dimethylamino-1,3,4-oxadiazol-2yl or 5-methylamino-1,3,4-thiadiazol-2-yl, where the wavy line indicates the point of attachment to the rest of the molecule. The notation  means

Y^1 can be attached to the rest of the molecule at any of the available positions of the Y^1 group set forth above. For example,  is meant to include 5H-pyrrolo[2,3-b]pyrazin-2-yl, 5H-pyrrolo[2,3-b]pyrazin-3-yl, 5H-pyrrolo[2,3-b]pyrazin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-6-yl, 5H-pyrrolo[2,3-b]pyrazin-7-yl, (i.e., substitutions can be at 2, 3, 5, 6, or 7 positions of the 5H-pyrrolo[2,3-b]pyrazine ring). All the other variables Y^2, Q, Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0079] In some embodiments of compounds of formula (I), Y^1 is CN, halogen, -OH, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{1-6}haloalkyl, or optionally substituted C_{1-6}haloalkoxy. In other embodiments, Y^1 is CN, halogen, -OH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6}haloalkyl or C_{1-6}haloalkoxy, each of which is optionally substituted with from 1 to 3 R^1 substituents; or 1 to 3 R^a substituents; or 1 to 3 R^b substituents; or 1 to 3 R^c substituents; or 1 to 3 R^d substituents; or 1 to 3 R^e substituents; 1 to 3 R^f substituents; or 1 to 3 substituents selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido or methylcarbamoyl. In some embodiments, Y^1 is CN, halogen, -OH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6}haloalkyl or C_{1-6}haloalkoxy. In other embodiments, Y^1 is CN, Cl, Br, F, I, -OH, $-OCH_3$, $-CF_3$, or $-OCF_3$, each of which is optionally substituted with from 1 to 3 R^1 substituents; or 1 to 3 R^a substituents; or 1 to 3 R^b substituents; or 1 to 3 R^c substituents; or 1 to 3 R^d substituents; or 1 to 3 R^e substituents; 1 to 3 R^f substituents; or 1 to 3 substituents selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino, 1-hydroxy-1-methylethyl, methylcarbamoyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl, 1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cycloheyloxy, 4-morpholino, 4-hydroxypiperidinyl,1- piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-t-butoxycarbonylpiperazinyl, azetidinyl, pyrrolidinyl, cyclopropylcarbamoyl, 5-methyl-1,2,4-oxadiazol-3-yl, 5-methyl-1,3,4-oxadiazol-2yl, 5-dimethylamino-1,3,4-oxadiazol-2yl or 5-methylamino-1,3,4-thiadiazol-2-yl, In other embodiments, Y^1 is CN, halogen, -OH, CH_3, CH_3O-, CF_3, CF_3O, cyclopropyl or cyclopropylmethyl. All the other variables Y^2, Q, Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0080] In any of embodiments of compounds of formula (I) above and described herein, where appropriate, each R^1 is independently selected from halogen, -CN, -OH, $-CF_3$, CF_3O-, C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}cycloalkoxy, $-NO_2$, benzyl, phenyl, cyclopropyl, cyclopropylmethyl, 1-cycanocyclopropyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl,

1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cycloheyloxy, C_{1-6}alkyl-1,2,4-oxadiazol-3-yl, 5-C_{1-6}alkyl-1,3,4-oxadiazol-2yl, 5-di(C_{1-6}alkyl)amino-1,3,4-oxadiazol-2yl, 5-C_{1-6}alkylamino-1,3,4-thiadiazol-2-yl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexymethyl, -OC(O)R^b, -C(O)R^b, -C(O)OR^b, -NHC(O)R^b, -C(O)NHR^b, -NHR^b or –N$R^b$$R^b$. In certain instances, R^1 is F, Cl, Br, I, -CN, -OH, -CF_3, NH_2, CF_3O-, CH_3-, CH_3O, C_2H_5O-, -NO_2, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl, 1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cycloheyloxy, 4-morpholino, 4-hydroxypiperidinyl,1- piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-t-butoxycarbonylpiperazinyl, azetidinyl, pyrrolidinyl, cyclopropylcarbamoyl, 5-methyl-1,2,4-oxadiazol-3-yl, 5-methyl-1,3,4-oxadiazol-2yl, 5-dimethylamino-1,3,4-oxadiazol-2yl, 1,3,4-thiadiazol-2-yl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl.

[0081] In some embodiments of compounds of formula (I), Y^1 is selected from the group consisting of 5-pyrimidinyl, 2-pyrimidinyl, 4-pyrimidinyl, 2-methoxy-5-pyrimidinyl, 2-methoxy-3-pyrimidinyl, 2-methoxy-4-pyrimidinyl, 4-methoxy-2-pyrimidinyl, 4-methoxy-4-pyrimidinyl, 4-methoxy-5-pyrimidinyl, 5-methoxy-2-pyrimidinyl, 5-methoxy-4-pyrimidinyl, 2-cyclopropyl-5-pyrimidinyl, 2-cyclopropyl-3-pyrimidinyl, 2-cyclopropyl-4-pyrimidinyl, 4-cyclopropyl-2-pyrimidinyl, 4-cyclopropyl-4-pyrimidinyl, 4-cyclopropyl-5-pyrimidinyl, 5-cyclopropyl-2-pyrimidinyl, 5-cyclopropyl-4-pyrimidinyl, 2-cyclopropylmethyl-5-pyrimidinyl, 2-cyclopropylmethyl-3-pyrimidinyl, 2-cyclopropylmethyl-4-pyrimidinyl, 4-cyclopropylmethyl-2-pyrimidinyl, 4-cyclopropylmethyl-4-pyrimidinyl, 4-cyclopropylmethyl-5-pyrimidinyl, 5-cyclopropylmethyl-2-pyrimidinyl, 5-cyclopropylmethyl-4-pyrimidinyl, 2-methyl-5-pyrimidinyl, 2-methyl-3-pyrimidinyl, 2-methyl-4-pyrimidinyl, 4-methyl-2-pyrimidinyl, 4-methyl-4-pyrimidinyl, 4-methyl-5-pyrimidinyl, 5-methyl-2-pyrimidinyl, 5-methyl-4-pyrimidinyl, 2-halo-5-pyrimidinyl, 2-halo-3-pyrimidinyl, 2-halo-4-pyrimidinyl, 4-halo-2-pyrimidinyl, 4-halo-4-pyrimidinyl, 4-halo-5-pyrimidinyl, 5-halo-2-pyrimidinyl, 5-halo-4-pyrimidinyl, 2-(1-cyanocyclopropyl)-5-pyrimidinyl, 2-(1-cyanocyclopropyl)-3-pyrimidinyl, 2-(1-cyanocyclopropyl)-4-pyrimidinyl, 4-(1-cyanocyclopropyl)-2-pyrimidinyl, 4-(1-cyanocyclopropyl)-4-pyrimidinyl, 4-(1-cyanocyclopropyl)-5-pyrimidinyl, 5-(1-cyanocyclopropyl)-2-pyrimidinyl, 5-(1-cyanocyclopropyl)-4-pyrimidinyl, 2-cyclopropylamino-5-pyrimidinyl, 2-cyclopropylamino-3-pyrimidinyl, 2-cyclopropylamino-4-pyrimidinyl, 4-cyclopropylamino-2-pyrimidinyl, 4-cyclopropylamino-4-pyrimidinyl, 4-cyclopropylamino-5-pyrimidinyl, 5-cyclopropylamino-2-pyrimidinyl, 5-cyclopropylamino-4-pyrimidinyl, 2-dimethylamino-5-pyrimidinyl, 2-dimethylamino-3-pyrimidinyl, 2-dimethylamino-4-pyrimidinyl, 4-dimethylamino-2-pyrimidinyl, 4-dimethylamino-4-pyrimidinyl, 4-dimethylamino-5-pyrimidinyl, 5-dimethylamino-2-

pyrimidinyl, 5-dimethylamino-4-pyrimidinyl, 2-cyano-5-pyrimidinyl, 2-cyano-3-pyrimidinyl, 2-cyano-4-pyrimidinyl, 4-cyano-2-pyrimidinyl, 4-cyano-4-pyrimidinyl, 4-cyano-5-pyrimidinyl, 5-cyano-2-pyrimidinyl, 5-cyano-4-pyrimidinyl, 2-trifluoromethyl-5-pyrimidinyl, 2-trifluoromethyl-3-pyrimidinyl, 2-trifluoromethyl-4-pyrimidinyl, 4-trifluoromethyl-2-pyrimidinyl, 4-trifluoromethyl-4-pyrimidinyl, 4- trifluoromethyl-5-pyrimidinyl, 5-trifluoromethyl-2-pyrimidinyl, 5-trifluoromethyl-4-pyrimidinyl, 2-trifluoromethoxy-5-pyrimidinyl, 2-trifluoromethoxy-3-pyrimidinyl, 2-trifluoromethoxy-4-pyrimidinyl, 4-trifluoromethoxy-2-pyrimidinyl, 4-trifluoromethoxy-4-pyrimidinyl, 4- trifluoromethoxy-5-pyrimidinyl, 5-trifluoromethoxy-2-pyrimidinyl, 5-trifluoromethoxy-4-pyrimidinyl, 2-hydroxy-5-pyrimidinyl, 2-hydroxy-3-pyrimidinyl, 2-hydroxy-4-pyrimidinyl, 4-hydroxy-2-pyrimidinyl, 4-hydroxy-4-pyrimidinyl, 4-hydroxy-5-pyrimidinyl, 5-hydroxy-2-pyrimidinyl, 5-hydroxy-4-pyrimidinyl, 2-amino-5-pyrimidinyl, 2-amino-3-pyrimidinyl, 2-amino-4-pyrimidinyl, 4-amino-2-pyrimidinyl, 4-amino-4-pyrimidinyl, 4-amino-5-pyrimidinyl, 5-amino-2-pyrimidinyl, 5-amino-4-pyrimidinyl, 2-methylamino-5-pyrimidinyl, 2-methylamino-3-pyrimidinyl, 2-methylamino-4-pyrimidinyl, 4-methylamino-2-pyrimidinyl, 4-methylamino-4-pyrimidinyl, 4-methylamino-5-pyrimidinyl, 5-methylamino-2-pyrimidinyl, 5-methylamino-4-pyrimidinyl, 2-dimethylamino-5-pyrimidinyl, 2-dimethylamino-3-pyrimidinyl, 2-dimethylamino-4-pyrimidinyl, 4-dimethylamino-2-pyrimidinyl, 4-dimethylamino-4-pyrimidinyl, 4-dimethylamino-5-pyrimidinyl, 5-dimethylamino-2-pyrimidinyl, 5-dimethylamino-4-pyrimidinyl, 2-acetamido-5-pyrimidinyl, 2-acetamido-3-pyrimidinyl, 2-acetamido-4-pyrimidinyl, 4-acetamido-2-pyrimidinyl, 4-acetamido-4-pyrimidinyl, 4-acetamido-5-pyrimidinyl, 5-acetamido-2-pyrimidinyl, 5-acetamido-4-pyrimidinyl, 2-methylthio-5-pyrimidinyl, 2-methylthio-3-pyrimidinyl, 2-methylthio-4-pyrimidinyl, 4-methylthio-2-pyrimidinyl, 4-methylthio-4-pyrimidinyl, 4-methylthio-5-pyrimidinyl, 5-methylthio-2-pyrimidinyl, 5-methylthio-4-pyrimidinyl, 2-acetoxy-5-pyrimidinyl, 2-acetoxy-3-pyrimidinyl, 2-acetoxy-4-pyrimidinyl, 4-acetoxy-2-pyrimidinyl, 4-acetoxy-4-pyrimidinyl, 4-acetoxy-5-pyrimidinyl, 5-acetoxy-2-pyrimidinyl, 5-acetoxy-4-pyrimidinyl, 2-acetyl-5-pyrimidinyl, 2-acetyl-3-pyrimidinyl, 2-acetyl-4-pyrimidinyl, 4-acetyl-2-pyrimidinyl, 4-acetyl-4-pyrimidinyl, 4-acetyl-5-pyrimidinyl, 5-acetyl-2-pyrimidinyl, 5-acetyl-4-pyrimidinyl, 2-methoxycarbonyl-5-pyrimidinyl, 2-methoxycarbonyl-3-pyrimidinyl, 2-methoxycarbonyl-4-pyrimidinyl, 4-methoxycarbonyl-2-pyrimidinyl, 4-methoxycarbonyl-4-pyrimidinyl, 4-methoxycarbonyl-5-pyrimidinyl, 5-methoxycarbonyl-2-pyrimidinyl, 5-methoxycarbonyl-4-pyrimidinyl, 2-methylcarbamoyl-5-pyrimidinyl, 2-methylcarbamoyl-3-pyrimidinyl, 2-methylcarbamoyl-4-pyrimidinyl, 4-methylcarbamoyl-2-pyrimidinyl, 4-methylcarbamoyl-4-pyrimidinyl, 4-methylcarbamoyl-5-pyrimidinyl, 5-methylcarbamoyl-2-pyrimidinyl, 5-methylcarbamoyl-4-pyrimidinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 3-methoxy-2-pyridyl, 4-methoxy-2-pyridyl, 5-methoxy-2-pyridyl, 6-methoxy-2-pyridyl, 2-methoxy-3-pyridyl, 4-methoxy-3-pyridyl, 5-methoxy-3-pyridyl, 6-methoxy-3-pyridyl, 2-methoxy-4-pyridyl, 3-methoxy-4-pyridyl, 3-halo-2-pyridyl, 4-halo-2-pyridyl, 5-halo-2-pyridyl, 6-halo-2-pyridyl, 2-halo-3-pyridyl, 4-halo-3-pyridyl, 5-halo-3-pyridyl, 6-halo-3-pyridyl, 2-halo-4-pyridyl, 3-halo-4-pyridyl, 3-cyano-2-pyridyl, 4-cyano-2-pyridyl, 5-cayno-2-pyridyl, 6-cyano-2-pyridyl, 2-cyano-3-

pyridyl, 4-cyano-3-pyridyl, 5-cyano-3-pyridyl, 6-cyano-3-pyridyl, 2-cyano-4-pyridyl, 3-cyano-4-pyridyl, 3-hydroxy-2-pyridyl, 4-hydroxy-2-pyridyl, 5-hydroxy-2-pyridyl, 6-hydroxy-2-pyridyl, 2-hydroxy-3-pyridyl, 4-hydroxy-3-pyridyl, 5-hydroxy-3-pyridyl, 6-hydroxy-3-pyridyl, 2-hydroxy-4-pyridyl, 3-hydroxy-4-pyridyl, 3-trifluoromethyl-2-pyridyl, 4-trifluoromethyl-2-pyridyl, 5-trifluoromethyl-2-pyridyl, 6-trifluoromethyl-2-pyridyl, 2-trifluoromethyl-3-pyridyl, 4-trifluoromethyl-3-pyridyl, 5-trifluoromethyl-3-pyridyl, 6-trifluoromethyl-3-pyridyl, 2-trifluoromethyl-4-pyridyl, 3-trifluoromethyl-4-pyridyl, 3-amino-2-pyridyl, 4-amino-2-pyridyl, 5-amino-2-pyridyl, 6-amino-2-pyridyl, 2-amino-3-pyridyl, 4-amino-3-pyridyl, 5-amino-3-pyridyl, 6-amino-3-pyridyl, 2-amino-4-pyridyl, 3-amino-4-pyridyl, 3-trifluoromethoxy-2-pyridyl, 4-trifluoromethoxy-2-pyridyl, 5-trifluoromethoxy-2-pyridyl, 6-trifluoromethoxy-2-pyridyl, 2-trifluoromethoxy-3-pyridyl, 4-trifluoromethoxy-3-pyridyl, 5-trifluoromethoxy-3-pyridyl, 6-trifluoromethoxy-3-pyridyl, 2-trifluoromethoxy-4-pyridyl, 3-trifluoromethoxy-4-pyridyl, 3-methyl-2-pyridyl, 4-methyl-2-pyridyl, 5-methyl-2-pyridyl, 6-methyl-2-pyridyl, 2-methyl-3-pyridyl, 4-methyl-3-pyridyl, 5-methyl-3-pyridyl, 6-methyl-3-pyridyl, 2-methyl-4-pyridyl, 3-methyl-4-pyridyl, 3-methoxy-2-pyridyl, 4-methoxy-2-pyridyl, 5-methoxy-2-pyridyl, 6-methoxy-2-pyridyl, 2-methoxy-3-pyridyl, 4-methoxy-3-pyridyl, 5-methoxy-3-pyridyl, 6-methoxy-3-pyridyl, 2-methoxy-4-pyridyl, 3-methoxy-4-pyridyl, 3-cyclopropyl-2-pyridyl, 4-cyclopropyl-2-pyridyl, 5-cyclopropyl-2-pyridyl, 6-cyclopropyl-2-pyridyl, 2-cyclopropyl-3-pyridyl, 4-cyclopropyl-3-pyridyl, 5-cyclopropyl-3-pyridyl, 6-cyclopropyl-3-pyridyl, 2-cyclopropyl-4-pyridyl, 3-cyclopropyl-4-pyridyl, 3-cyclopropylmethyl-2-pyridyl, 4-cyclopropylmethyl-2-pyridyl, 5-cyclopropylmethyl-2-pyridyl, 6-cyclopropylmethyl-2-pyridyl, 2-cyclopropylmethyl-3-pyridyl, 4-cyclopropylmethyl-3-pyridyl, 5-cyclopropylmethyl-3-pyridyl, 6-cyclopropylmethyl-3-pyridyl, 2-cyclopropylmethyl-4-pyridyl, 3-cyclopropylmethyl-4-pyridyl, 3-cyclopropylamino-2-pyridyl, 4-cyclopropylamino-2-pyridyl, 5-cyclopropylamino2-pyridyl, 6-cyclopropylamino-2-pyridyl, 2-cyclopropylamino-3-pyridyl, 4-cyclopropylamino-3-pyridyl, 5-cyclopropylamino-3-pyridyl, 6-cyclopropylamino-3-pyridyl, 2-cyclopropylamino-4-pyridyl, 3-cyclopropylamino-4-pyridyl, 3-cyclopropylmethylamino-2-pyridyl, 4-cyclopropylmethylamino-2-pyridyl, 5-cyclopropylmethylamino-2-pyridyl, 6-cyclopropylmethylamino-2-pyridyl, 2-cyclopropylmethylamino-3-pyridyl, 4-cyclopropylmethylamino-3-pyridyl, 5-cyclopropylmethylamino-3-pyridyl, 6-cyclopropylmethylamino-3-pyridyl, 2-cyclopropylmethylamino-4-pyridyl, 3-cyclopropylmethylamino-4-pyridyl, 3-methylamino-2-pyridyl, 4-methylamino-2-pyridyl, 5-methylamino-2-pyridyl, 6-methylamino-2-pyridyl, 2-methylamino-3-pyridyl, 4-methylamino-3-pyridyl, 5-methylamino-3-pyridyl, 6-methylamino-3-pyridyl, 2-methylamino-4-pyridyl, 3-methylamino-4-pyridyl, 3-dimethylamino-2-pyridyl, 4-dimethylamino-2-pyridyl, 5-dimethylamino-2-pyridyl, 6-dimethylamino-2-pyridyl, 2-dimethylamino-3-pyridyl, 4-dimethylamino-3-pyridyl, 5-dimethylamino-3-pyridyl, 6-dimethylamino-3-pyridyl, 2-dimethylamino-4-pyridyl, 3-dimethylamino-4-pyridyl, 3-methylthio-2-pyridyl, 4-methylthio-2-pyridyl, 5-methylthio-2-pyridyl, 6-methylthio-2-pyridyl, 2-methylthio-3-pyridyl, 4-methylthio-3-pyridyl, 5-methylthio-3-pyridyl, 6-methylthio-3-pyridyl, 2-methylthio-4-pyridyl, 3-methylthio-4-pyridyl, 3-acetoxy-2-pyridyl,

4-acetoxy-2-pyridyl, 5-acetoxy-2-pyridyl, 6-acetoxy-2-pyridyl, 2-acetoxy-pyridyl, 4-acetoxy-3-pyridyl, 5-acetoxy-3-pyridyl, 6-acetoxy-3-pyridyl, 2-acetoxy-4-pyridyl, 3-acetoxy-4-pyridyl, 3-acetyl-2-pyridyl, 4-acetyl-2-pyridyl, 5-acetyl-2-pyridyl, 6-acetyl-2-pyridyl, 2-acetyl-pyridyl, 4-acetyl-3-pyridyl, 5-acetyl-3-pyridyl, 6-acetyl-3-pyridyl, 2-acetyl-4-pyridyl, 3-acetyl-4-pyridyl, 3-methoxycarbonyl-2-pyridyl, 4-methoxycarbonyl-2-pyridyl, 5-methoxycarbonyl-2-pyridyl, 6-methoxycarbonyl-2-pyridyl, 2-methoxycarbonyl-3-pyridyl, 4-methoxycarbonyl-3-pyridyl, 5-methoxycarbonyl-3-pyridyl, 6-methoxycarbonyl-3-pyridyl, 2-methoxycarbonyl-4-pyridyl, 3-methoxycarbonyl-4-pyridyl, 3-methylcarbamoyl-2-pyridyl, 4-methylcarbamoyl-2-pyridyl, 5-methylcarbamoyl-2-pyridyl, 6-methylcarbamoyl-2-pyridyl, 2-methylcarbamoyl-3-pyridyl, 4-methylcarbamoyl-3-pyridyl, 5-methylcarbamoyl-3-pyridyl, 6-methylcarbamoyl-3-pyridyl, 2-methylcarbamoyl-4-pyridyl, 3-methylcarbamoyl-4-pyridyl, 3-acetamido-2-pyridyl, 4-acetamido-2-pyridyl, 5-acetamido-2-pyridyl, 6-acetamido-2-pyridyl, 2-acetamido-3-pyridyl, 4-acetamido-3-pyridyl, 5-acetamido-3-pyridyl, 6-acetamido-3-pyridyl, 2-acetamido-4-pyridyl and 3-acetamido-4-pyridyl, 3-(1-cyanocyclopropyl)-2-pyridyl, 4-(1-cyanocyclopropyl)-2-pyridyl, 5-(1-cyanocyclopropyl)-2-pyridyl, 6-(1-cyanocyclopropyl)-2-pyridyl, 2-(1-cyanocyclopropyl)-3-pyridyl, 4-(1-cyanocyclopropyl)-3-pyridyl, 5-(1-cyanocyclopropyl)-3-pyridyl, 6-(1-cyanocyclopropyl)-3-pyridyl, 2-(1-cyanocyclopropyl)-4-pyridyl, 3-(1-cyanocyclopropyl)-4-pyridyl, each of which is optionally substituted with from 1, 2, or 3 susbtituents independently selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, 1-cyanocyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl. In some instances, the 1, 2, 3 substituents are on the aromatic portion of Y^1. In other instances, the 1, 2, 3 substituents are on the aliphatic portion of Y^1. All the other variables Y^2, Q, Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0082] In certain embodiments of compounds of formula (I), Y^1 is phenyl substituted with from 1 to 2 susbtituents independently selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, C_2H_5O-, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl, 1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cyclohcyloxy, 4-morpholino, 4-hydroxypiperidinyl,1- piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-t-butoxycarbonylpiperazinyl, azetidinyl, pyrrolidinyl, cyclopropylcarbamoyl, 5-methyl-1,2,4-oxadiazol-3-yl, 5-methyl-1,3,4-oxadiazol-2yl, 5-dimethylamino-1,3,4-oxadiazol-2yl, 5-methylamino-1,3,4-thiadiazol-2-yl, methylamino methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl.

[0083] In other embodiments of compounds of formula (I), Y^1 is selected from the group consisting of phenyl, 2-halophenyl, 3-halophenyl, 4-halophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-aminophenyl, 3-aminophenyl, 4-aminophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-cyclopropylphenyl, 3-cyclopropylphenyl, 4-cyclopropylphenyl, 2-cyclopropylmethylphenyl, 3- cyclopropylmethylphenyl, 4-cyclopropylmethylphenyl, 2-cyclopropylmethylaminophenyl, 3- cyclopropylmethylaminophenyl, 4-cyclopropylmethylaminophenyl, 2-cyclopropylaminophenyl, 3-cyclopropylaminophenyl, 4-cyclopropylaminophenyl, 2-methylaminophenyl, 3-methylaminophenyl, 4-methylaminophenyl, 2-dimethylaminophenyl, 3-dimethylaminophenyl, 4-dimethylaminophenyl, 2-methylthiophenyl, 3-methylthiophenyl, 4-methylthiophenyl, 2-acetoxyphenyl, 3-acetoxyphenyl, 4-acetoxyphenyl, 2-acetylphenyl, 3-acetylphenyl, 4-acetylphenyl, 2-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methoxycarbonylphenyl, 2-acetamidophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 2-methylcarbamoylphenyl, 3-methylcarbamoylphenyl, 4-methylcarbamoylphenyl, 2-(1-cyanocyclopropyl)phenyl, 3-(1-cyanocyclopropyl)phenyl and 4-(1-cyanocyclopropyl)phenyl, each of which is optionally substituted with from 1, 2 or susbtituents independently selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, 1-cyanocyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl or methylcarbamoyl. In some instances, the 1, 2, 3 substituents are on the aromatic portion of Y^1. In other instances, the 1, 2, 3 substituents are on the aliphatic portion of Y^1. All the other variables Y^2, Q, Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0084] In some embodiments of compounds of formula (I), Y^2 is as defined in the summary of the invention and the other variables Y^1, Q and Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the above embodiments and any of the embodiments described herein.

[0085] In some embodiments of compounds of formula (I), Y^2 is H, halogen, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}cycloalkylamino, C_{3-6}cycloalkyl-C_{1-3}alkylamino, aryl, heteroaryl, arylalkyl or heteroarylalkyl, wherein the aliphatic or aromatic portion of Y^2 is optionally substituted with 1, 2 or 3 substituents independently selected from H, F, Cl, I, CN, CH_3, CH_3O-, phenyl, CF_3 or CF_3O. In certain instances, Y^2 is H, halogen, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}cycloalkylamino or C_{3-6}cycloalkyl-C_{1-3}alkylamino, wherein the aliphatic portion of Y^2 is optionally substituted with 1, 2 or 3 substituents independently selected from H, F, Cl, I, CN, CH_3, CH_3O-, phenyl, CF_3 or CF_3O. All other variables Y^1, Q and Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0086] In some embodiments of compounds of formula (I), Y^2 is H, F, Cl, I, CN, CH_3, CH_3O-, cyclopropylamino or cyclopropylmethylamino. All the other variables Y^1, Q and Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0087] In some preferred embodiments of compounds of formula (I), Y^2 is H and all the other variables Y^1, Q and Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0088] In some embodiments of compounds of formula (I), Q is selected from H, F, Cl or CH_3. In one embodiment, Q is H. In another embodiment, Q is F. In yet another embodiment, Q is CH_3. In still other embodiment, Q is Cl. In another embodiment, Q is H or F. All the other variables Y^1, Y^2, Z of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0089] In some embodiments of compounds of formula (I), Z is as defined in the summary of invention. All the other variables of formula (I) and R^4, R^5, R^6, R^7 and R^8 are as defined in any of the embodiments described herein.

[0090] In some embodiments of compounds of formula (I), Z is $-N(R^4)(R^5)$ or $-C(R^6)(R^7)(R^8)$, wherein R^4 and R^5 are each independently selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted C_{3-8}cycloalkylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl; or R^4 and R^5 taken together with the nitrogen atom to which they are attached form a four to eight-membered ring having from 0-2 additional heteroatoms as ring members selected from N, O or S, wherein the four to eight-membered ring is optionally substituted with from one to three groups independently selected from C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylalkyl, aryl, arylalkyl or R^e. R^6, R^7 and R^8 are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkylalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl or $-X^2R^9$; wherein the aliphatic or aromatic portion of R^6, R^7 and R^8 are each optionally substituted with from 1 to 3 members independently selected from the group consisting of C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl and R^e; or any two of the R^6, R^7 and R^8 groups taken together with the carbon atom to which they are attached form a 3 to 8-membered carbocyclic ring or a 4 to 8-membered heterocyclic ring having from 1 to 2 heteroatoms as ring members selected from N, O or S, wherein the 3 to 8-membered carbocyclic ring or the 4 to 8-membered heterocyclic ring is optionally substituted with from one to three groups independently selected from C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or R^e, provided at each occurrence, at least two of the R^6, R^7 and R^8 groups are not simultaneously hydrogen. All the other variables Y^1, Y^2 and Q of formula (I) are as defined in any of the embodiments described herein.

[0091] In some embodiments of compounds of formula (I), Z is $-N(R^4)(R^5)$, wherein R^4 and R^5 are each independently selected from C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, aryl-C_{1-4}alkyl, heteroaryl or heteroaryl-C_{1-4}alkyl, each of which is optionally substituted with from (i) 1-3 substituents independently selected from C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or R^e; or (ii) 1, 2 or 3 R^a substituents; or (iii) 1, 2 or 3 R^b substituents; or (iv) 1, 2 or 3 R^c substituents; or (v) 1, 2 or 3 R^d substituents; or (vi) 1, 2 or 3 R^f groups. All the other variables Y^1, Y^2 and Q of formula (I) are as defined in any of the embodiments described herein.

[0092] In some embodiments of compounds of formula (I), R^4 is $-CH_3$ and R^5 is C_{2-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, aryl-C_{1-4}alkyl, heteroaryl or heteroaryl-C_{1-4}alkyl, each of which is optionally substituted with from (i) 1-3 substituents independently selected from C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or R^e; or (ii) 1, 2 or 3 R^a substituents; or (iii) 1, 2 or 3 R^b substituents; or (iv) 1, 2 or 3 R^c substituents; or (v) 1, 2 or 3 R^d substituents; or (vi) 1, 2 or 3 R^f groups. In certain instances, R^4 is $-CH_3$ and R^5 is C_{2-6}alkyl. All the other variables Y^1, Y^2 and Q of formula (I) are as defined in any of the embodiments described herein.

[0093] In some embodiments of compounds of formula (I), R^4 and R^5 are each independently selected from C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, aryl-C_{1-4}alkyl, heteroaryl or heteroaryl-C_{1-4}alkyl, each of which is optionally substituted with from 1, 2 or 3 R^x members selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-oxetanyl, 3-oxtetanyl, 2-oxetanylmethyl, 3-oxtetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 4-morpholinyl, 2-morpholinyl or 3- morpholinyl. In certain instances, R^x is F, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-oxetanyl, 3-oxtetanyl, 2-oxetanylmethyl, 3-oxtetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 4-morpholinyl, 2-morpholinyl or 3- morpholinyl. All the other variables Y^1, Y^2 and Q of formula (I) are as defined in any of the embodiments described herein.

[0094] In some embodiments of compounds of formula (I), R^4 is $-CH_3$ and R^5 is C_{2-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, aryl-C_{1-4}alkyl, heteroaryl or heteroaryl-C_{1-4}alkyl, each of which is optionally substituted with from 1, 2 or 3 R^x members selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-oxetanyl, 3-oxtetanyl, 2-oxetanylmethyl, 3-oxtetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 4-morpholinyl, 2-morpholinyl or 3- morpholinyl. In certain instances, R^x is F, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-oxetanyl, 3-oxtetanyl, 2-oxetanylmethyl, 3-oxtetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 4-morpholinyl, 2-morpholinyl or 3- morpholinyl. All the other variables Y^1, Y^2 and Q of formula (I) are as defined in any of the embodiments described herein.

[0095] In some embodiments of compounds of formula (I), R^4 is $-CH_3$ and R^5 is selected from ethyl, propyl, butyl, pentyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, phenyl or benzyl, each of which is optionally substituted with from 1-3 substituents independently selected from F, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-oxetanyl, 3-oxtetanyl, 2-oxetanylmethyl, 3-oxtetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 4-morpholinyl, 2-morpholinyl or 3-morpholinyl. All the other variables Y^1, Y^2 and Q of formula (I) are as defined in any of the embodiments described herein.

[0096] In some embodiments of compounds of formula (I), Z is $-N(R^4)(R^5)$, wherein $-N(R^4)(R^5)$ is selected from 1-azetindinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 4-thiomorpholinyl, 3-oxazolidinyl, 3-thiazolidinyl, 2-isoxazolidinyl, 2-isothiazolidinyl, 1-pyrazolidinyl, 1-piperazinyl, 1-hexahydropyrimidinyl or 1-hexahydropyridazinyl, each of which is (i) optionally substituted with from 1 to 3 R^{26} substituents independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and R^e; or (ii) two

adjacent R^{26} substituents together with the atom to which they are attached form a 5 or 6-membered aromatic ring having from 0 to 2 additional atoms as ring members selected from O, N or S or (iii) optionally substituted with from 1 to 8 deuteriums with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. In certain instances, R^{26} is F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-oxetanyl, 3-oxtetanyl, 2-oxetanylmethyl, 3-oxtetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 4-morpholinyl, 2-morpholinyl or 3- morpholinyl. In other instances, R^{26} is F, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-oxetanyl, 3-oxtetanyl, 2-oxetanylmethyl, 3-oxtetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 4-morpholinyl, 2-morpholinyl or 3- morpholinyl. In other instances, R^{26} is F, CH_3, methoxycarbonyl, ethoxycarbonyl, $-CH_3$, $CH_3(CO)NH$-, vinyl, propen-3-yl or $CH_3(CO)(CH_3)N$-. In some embodiments, each hydrogen atom in Z is optionally replaced by a deuterium atom with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. All the other variables Y^1, Y^2 and Q of formula (I) are as defined in any of the embodiments described herein.

[0097] In some embodiments of compounds of formula (I), Z is $-C(R^6)(R^7)(R^8)$, where R^6 is H and R^7 and R^8 are each independently C_{1-6}alkyl, optionally substituted with from 1 to 3 R^d or R^e. In some embodiments, R^6, R^7 and R^8 are each independently C_{1-6}alkyl, optionally substituted with from 1 to 3 R^d or R^e. In some embodiments, $-C(R^6)(R^7)(R^8)$ is cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, cycloheptyl, cyclooctyl, each of which is optionally substituted with from 1-3 R^{28} substituents independently selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-CH_2CH{=}CH_2$, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, vinyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-oxetanyl, 3-oxtetanyl, 2-oxetanylmethyl, 3-oxtetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 4-morpholinyl, 2-morpholinyl or 3- morpholinyl. In some instances, R^{28} is F, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino,

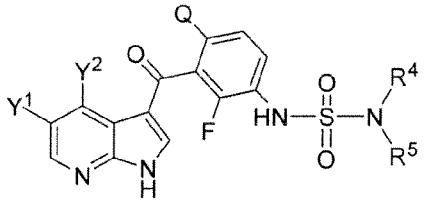
cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-oxetanyl, 3-oxtetanyl, 2-oxetanylmethyl, 3-oxtetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 4-morpholinyl, 2-morpholinyl or 3- morpholinyl. In some embodiments, $-C(R^6)(R^7)(R^8)$ is 2-azetindinyl, 3-azetindinyl, 3-pyrrolidinyl, 2-pyrrolidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2-morpholinyl, 3-morpholinyl, 2-thiomorpholinyl, 3-thiomorpholinyl, 2-oxazolidinyl, 4-oxazolidinyl, 5-oxazolidinyl, 2-thiazolidinyl, 4-thiazolidinyl, 5-thiazolidinyl, 3-isoxazolidinyl, 4-isoxazolidinyl, 5-isoxazolidinyl, 3-isothiazolidinyl, 4-isothiazolidinyl, 5-isothiazolidinyl, 3-pyrazolidinyl, 4-pyrazolidinyl, 2-piperazinyl, 2-hexahydropyrimidinyl, 4-hexahydropyrimidinyl, 5-hexahydropyrimidinyl, 3-hexahydropyridazinyl or 4-hexahydropyridazinyl, each of which is optionally substituted with 1 to 3 R^{28} substituents. In some embodiments, each hydrogen atom in Z is optionally replaced by a deuterium atom with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. All the other variables Y^1, Y^2 and Q of formula (I) are as defined in any of the embodiments described herein.

[0098] In some embodiments of compounds of formula (I), Z is selected from the group consisting of cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, cycloheptyl, cyclooctyl, 1-azetindinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 4-thiomorpholinyl 3-oxazolidinyl, 3-thiazolidinyl, 2-isoxazolidinyl, 2-isothiazolidinyl, 1-pyrazolidinyl, 1-piperazinyl, 1-hexahydropyrimidinyl, 1-hexahydropyridazinyl, $(CH_3)(CF_3CH_2)N$-, cycloproylmethylamino, sec-butyl, pentan-2-yl and pentan-3-yl, each of which is (i) optionally substituted with from one to three R^{27} substituents independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and R^c; or (ii) two adjacent R^{27} substituents together with the atom to which they are attached form a 5 or 6-membered aromatic ring having from 0 to 2 additional atoms as ring members selected from O, N or S; or (iii) optionally substituted with from 1 to 11 deuteriums having at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. In one embodiment, Z is cyclopropyl optionally substituted with 1 to 2 R^{27} groups. In another embodiment, Z is cyclopentyl optionally substituted with 1 to 2 R^{27} groups. In yet another embodiment Z is 1-pyrrolidinyl optionally substituted with 1 to 2 R^{27} groups. In other embodiment, Z is 1-piperidinyl optionally substituted with 1 to 2 R^{27} groups. In another embodiment, Z is 1-pyrrolidinyl, 3-fluoro-1-pyrrolidinyl, (3S)-3-fluoro-1-pyrrolidinyl, (3R)-3-fluoro-1-pyrrolidinyl, 3,3-difluoro-1-pyrrolidinyl, 3-C_{1-6}alkyl-C(O)-C_{1-6}alkyl-N-1-pyrrolidinyl, 3-C_{1-6}alkyl-C(O)NH-1-pyrrolidinyl, C_{1-6}alkoxycarbonyl-1-pyrrolidinyl or 3,3-dimethyl-1-pyrrolidinyl. In certain instances, R^{27} is F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino,

dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-oxetanyl, 3-oxtetanyl, 2-oxetanylmethyl, 3-oxtetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 4-morpholinyl, 2-morpholinyl or 3- morpholinyl. In one instance, R^{27} is -F, methoxycarbonyl, ethoxycarbonyl, $-CH_3$, $CH_3(CO)NH$-, vinyl, propen-3-yl or $CH_3(CO)(CH_3)N$-. In another instance, R^{27} is -F, methoxycarbonyl, ethoxycarbonyl, $-CH_3$, $CH_3(CO)NH$- or $CH_3(CO)(CH_3)N$-. In yet another instance, R^{27} is vinyl or propen-3-yl. All the other variables Y^1, Y^2 and Q of formula (I) are as defined in any of the embodiments described herein.

Subformulae of Formula I

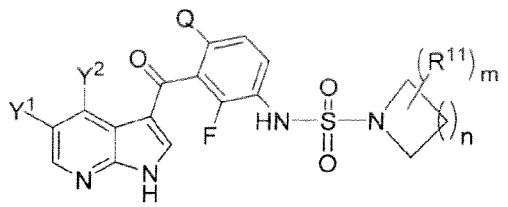
[0099] In one embodiment of the invention, compounds of formula (I) have subformula (Ia):



Ia

where the substituents Y^1, Y^2, Q, R^4 and R^5 are as defined in any of the embodiments disclosed herein. In some embodiments, R^4 is CH_3 and R^5 is $C_{2\text{-}6}$alkyl optionally substituted with from 1-3 substituents independently selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, -NO_2, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-oxetanyl, 3-oxtetanyl, 2-oxetanylmethyl, 3-oxtetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 4-morpholinyl, 2-morpholinyl or 3- morpholinyl.

[0100] In a second embodiment of the invention, compounds of formula (I) have subformula (Ib):

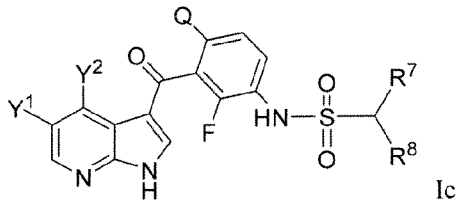


Ib

where R^{11} is $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$haloalkoxy, $C_{3\text{-}8}$cycloalkyl, $C_{3\text{-}8}$cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl or R^e, each of

which is optionally substituted with from (i) 1-3 substituents independently selected from C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, R^d or R^e; or (ii) 1, 2 or 3 R^a substituents; or (iii) 1, 2 or 3 R^b substituents; or (iv) 1, 2 or 3 R^c substituents; or (v) 1, 2 or 3 R^d substituents; or (vi) 1, 2 or 3 R^f groups; the subscript n is 1, 2, 3, 4 or 5 and the subscript m is 0, 1, 2 or 3. In some embodiments, R^{11} is C_{1-6}alkyl, F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, ethyl, propyl, butyl, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-oxetanyl, 3-oxtetanyl, 2-oxetanylmethyl, 3-oxtetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 4-morpholinyl, 2-morpholinyl or 3- morpholinyl. In some embodiments, m is 0. In other embodiments, the subscript n is 1, 2, 3 or 4. In some embodiments, n is 1, 2 or 3 and m is 1 or 2. All the other variables Y^1, Y^2 and Q are as defined in any of the embodiments described herein.

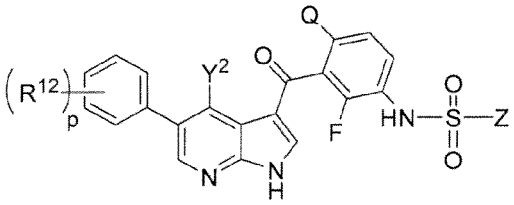
[0101] In a third embodiment of the invention, compounds of formula (I) have subformula (Ic):



Ic

wherein R^7 and R^8 are each independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or $-X^2R^9$, wherein the aliphatic or aromatic portion of R^7 and R^8 are each optionally substituted with from 1 to 3 members independently selected from the group consisting of C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and R^e; and wherein X^2 is $-NR^{10}$, O or S; R^{10} is H, C_{1-6}alkyl or aryl; and R^9 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, wherein R^9 is optionally substituted with from 1 to 3 R^e substituents. In some embodiments, R^7 and R^8 groups taken together with the carbon atom to which they are attached form a 3 to 8-membered carbocyclic ring or a 4 to 8-membered heterocyclic ring having from 1 to 2 heteroatoms as ring members selected from N, O or S, wherein the 3 to 8-membered carbocyclic ring or the 4 to 8-membered heterocyclic ring is optionally substituted with from one to three groups independently selected from C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or R^e. All the other variables Y^1, Y^2 and Q are as defined in any of the embodiments described herein.

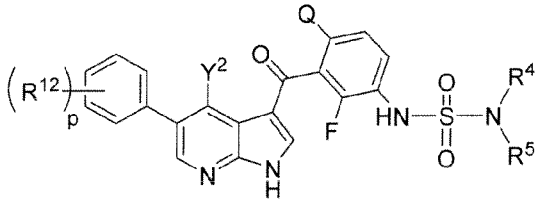
[0102] In a fourth embodiment of the invention, compounds of formula (I) have subformula (Id):



Id

wherein R^{12} is H or R^1; or two adjacent R^{12} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; wherein the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents, and the subscript p is an integer of 1 to 5. In one embodiment, p is 1. In another embodiment, p is 2. In yet another embodiment, p is 5 and two adjacent R^{12} substituents together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; wherein the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents, and each R^{12} is independently H, R^d or R^e. In some embodiments, the two adjacent R^{12} together with the atoms to which they are attached form an optionally substituted fused carbocyclic ring, including, but not limiting to, benzene, cyclopentane and cyclohexane rings. The substituents on the carbocyclic ring can be from 1-2 R^d or R^e groups. In other embodiments, two adjacent R^{12} together with the atoms to which they are attached form an optionally substituted fused heterocyclic ring, including, but not limiting to, pyrrole, furan, thiophen, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyridine, pyrazine, pyridazine, tetrahydrfuran, tetrahydropyran, tetrahydrothiophene, pyrazolidine, , isoxazolidine, imidazolidine, oxazolidine, thiazolidine, isothiazolidine, piperidine, piperazine, and hexahydropyrimidine rings. All the other variables Y^2, Q and Z are as defined in any of the embodiments described herein.

[0103] In a fifth embodiment of the invention, compounds of formula (I) have subformula (Id-1):

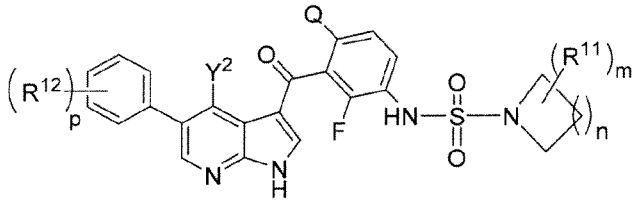


Id-1

wherein R^{12} is H or R^1; or two adjacent R^{12} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; wherein the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents, and the subscript p is an integer of 1 to 5. In one embodiment, p is 1. In another embodiment, p is 2. In yet another embodiment, p is 5 and two adjacent R^{12} substituents together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; wherein the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents, and the other three R^{12} is each independently H, R^d or R^e. In some embodiments, the two adjacent R^{12} together with the atoms to which they are attached form an optionally substituted fused carbocyclic

ring, including, but not limiting to, benzene, cyclopentane, cyclohexane and benzene rings. The substituents on the carbocyclic ring can be from 1-2 R^d or R^e groups. In other embodiments, two adjacent R^{12} together with the atoms to which they are attached form an optionally substituted fused heterocyclic ring, including, but not limiting to, pyrrole, furan, thiophen, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyridine, pyrazine, pyridazine, tetrahydrfuran, tetrahydropyran, tetrahydrothiophene, pyrazolidine, , isoxazolidine, imidazolidine, oxazolidine, thiazolidine, isothiazolidine, piperidine, piperazine, and hexahydropyrimidine rings. All the other variables Y^2, Q, R^4 and R^5 are as defined in any of the embodiments described herein.

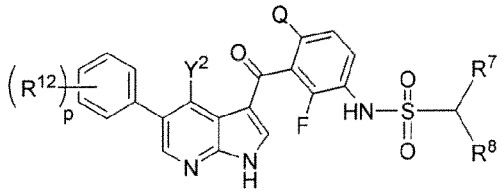
[0104] In a sixth embodiment of the invention, compounds of formula (I) have subformula (Id-2):



Id-2

All the variables R^{12}, p, m, n, Y^2, Q, and R^{11} are as defined in any of the embodiments described herein. In some embodiments, R^{11} is C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl or R^e, the subscript m is an integer from 0 to 3, and the subscript n is an integer from 1 to 5.

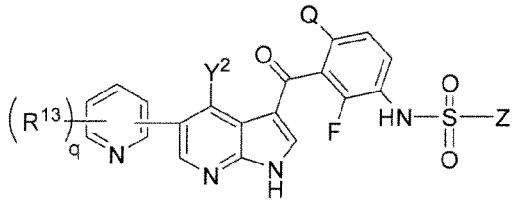
[0105] In a seventh embodiment of the invention, compounds of formula (I) have subformula (Id-3):



Id-3

All the variables R^{12}, p, Y^2, Q, R^7 and R^8 are as defined in any of the embodiments described herein. In some embodiments, R^7 and R^8 are each independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or $-X^2R^9$, wherein the aliphatic or aromatic portion of R^7 and R^8 are each optionally substituted with from 1 to 3 members independently selected from the group consisting of C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and R^e, provided at each occurrence, at least two of the R^6, R^7 and R^8 groups are not simultaneously hydrogen; and wherein X^2 is $-NR^{10}$, O or S; R^{10} is H, C_{1-6}alkyl or aryl; and R^9 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, wherein R^9 is optionally substituted with from 1 to 3 R^e substituents.

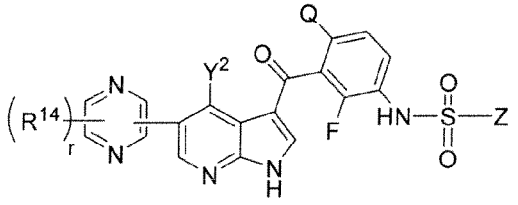
[0106] In an eighth embodiment of the invention, compounds of formula (I) have subformula (Ie):



Ie

wherein R^{13} is H or R^1; or two adjacent R^{13} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; and the subscript q is an integer of 1 to 4, where the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents. In one embodiment, q is 1. In another embodiment, q is 2. In yet another embodiment, q is 4 and two adjacent R^{13} substituents together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; wherein the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents, and the other two R^{13} groups are each independently H, R^d or R^e. In some embodiments, the two adjacent R^{13} together with the atoms to which they are attached form an optionally substituted fused carbocyclic ring, including, but not limiting to, benzene, cyclopentane and cyclohexane rings. The substituents on the carbocyclic ring can be from 1-2 R^d or R^e groups. In other embodiments, two adjacent R^{13} groups together with the atoms to which they are attached form an optionally substituted fused heterocyclic ring, including, but not limiting to, pyrrole, furan, thiophene, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyridine, pyrazine, pyridazine, tetrahydrfuran, tetrahydropyran, tetrahydrothiophene, pyrazolidine, , isoxazolidine, imidazolidine, oxazolidine, thiazolidine, isothiazolidine, piperidine, piperazine, and hexahydropyrimidine rings. All the other variables Y^2, Q and Z are as defined in any of the embodiments described herein.

[0107] In a ninth embodiment of the invention, compounds of formula (I) have subformula (If):

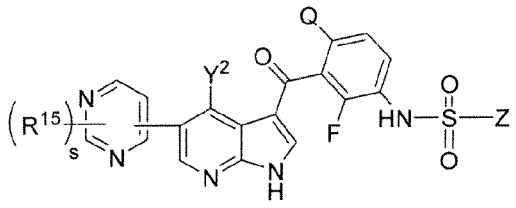


If

R^{14} is H or R^1; or two adjacent R^{14} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; and the subscript r is an integer of 1 to 3, where the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents. In one embodiment, r is 1. In another embodiment, r is 2. In yet another embodiment, r is 3 and two adjacent R^{14} substituents together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; wherein the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents, and the other R^{14} is H, R^d or R^e. In some embodiments, the two adjacent R^{14} together with the atoms to which they are attached form an optionally substituted fused carbocyclic ring, including, but not

limiting to, benzene, cyclopentane and cyclohexane rings. The substituents on the carbocyclic ring can be from 1-2 R^d or R^e groups. In other embodiments, two adjacent R^{14} groups together with the atoms to which they are attached form an optionally substituted fused heterocyclic ring, including, but not limiting to, pyrrole, furan, thiophene, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyridine, pyrazine, pyridazine, tetrahydrfuran, tetrahydropyran, tetrahydrothiophene, pyrazolidine, , isoxazolidine, imidazolidine, oxazolidine, thiazolidine, isothiazolidine, piperidine, piperazine, and hexahydropyrimidine rings. All the other variables Y^2, Q and Z are as defined in any of the embodiments described herein.

[0108] In a tenth embodiment of the invention, compounds of formula (I) have subformula (Ig):

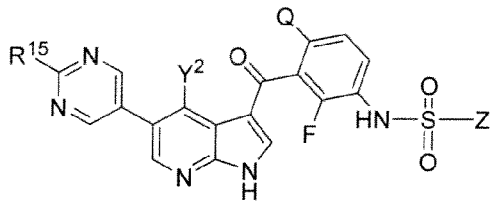


Ig

R^{15} is H or R^1; or two adjacent R^{15} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; and the subscript s is an integer of 1 to 3, where the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents. In one embodiment, s is 1. In another embodiment, s is 2. In yet another embodiment, s is 3 and two adjacent R^{15} substituents together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; wherein the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents, and the other R^{15} is H, R^d or R^e. In some embodiments, the two adjacent R^{15} together with the atoms to which they are attached form an optionally substituted fused carbocyclic ring, including, but not limiting to, benzene, cyclopentane and cyclohexane rings. The substituents on the carbocyclic ring can be from 1-2 R^d or R^e groups. In other embodiments, two adjacent R^{15} groups together with the atoms to which they are attached form an optionally substituted fused heterocyclic ring, including, but not limiting to, pyrrole, furan, thiophene, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyridine, pyrazine, pyridazine, tetrahydrfuran, tetrahydropyran, tetrahydrothiophene, pyrazolidine, isoxazolidine, imidazolidine, oxazolidine, thiazolidine, isothiazolidine, piperidine, piperazine, and hexahydropyrimidine rings. In other embodiments, R^{15} is halogen, -CN, -OH, $-CF_3$, CF_3O-, C_{1-6}alkyl, C_{1-6}alkoxy, $-NO_2$, benzyl, phenyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexymethyl, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ or $-NR^bR^b$. In some embodiments, R^{15} is F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido or methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-

cyclopropylethylamino or 1-hydroxy-1-methylethyl. All the other variables Y^2, Q and Z are as defined in any of the embodiments described herein.

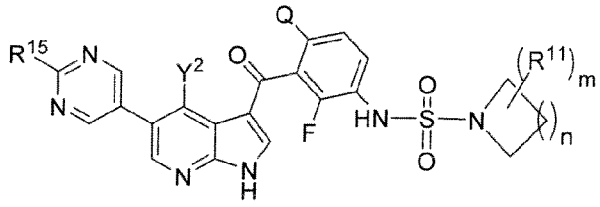
[0109] In an eleventh embodiment of the invention, compounds of formula (I) have subformula (Ig-1):



Ig-1

All the other variables R^{15}, Y^2, Q and Z are as defined in any of the embodiments described herein. In a preferred embodiment, Y^2 is H. In some embodiments, R^{15} is H or R^1. In some embodiments, R^{15} is R^a, R^b, R^c, R^d or R^e. In other embodiments, R^{15} is halogen, -CN, -OH, $-CF_3$, CF_3O-, C_{1-6}alkyl, C_{1-6}alkoxy, $-NO_2$, benzyl, phenyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexymethyl, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ or $-NR^bR^b$. In some embodiments, R^{15} is F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido or methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl. In some embodiments, Z is $-N(R^4)(R^5)$ or $-N(CH_3)(R^5)$. All the other variables are as defined in any of the embodiments described herein.

[0110] In a twelfth embodiment of the invention, compounds of formula (I) have subformula (Ig-2):

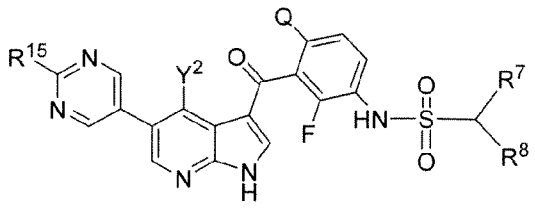


Ig-2

All the variables R^{15}, Y^2, Q, R^{11}, m and are as defined in any of the embodiments described herein. In a preferred embodiment, Y^2 is H. In some embodiments, R^{15} is H or R^1. In some embodiments, R^{15} is R^a, R^b, R^c, R^d or R^e. In one embodiment, R^{15} is C_{1-6}alkyl. In another embodiment, R^{15} is C_{3-6}cycloalkyl. In yet another embodiment, R^{15} is heterocycloalkyl. The subscript m is an integer from 0 to 3. The subscript n is an integer from 1 to 5. In some embodiments, m is 0. In other embodiments, the subscript n is 1, 2, 3 or 4. In some embodiments, n is 1, 2 or 3 and m is 1 or 2. In some embodiments, R^{11} is C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or R^e. In some embodiments, R^{11} is C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-}

$_6$haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl or R^e, each of which is optionally substituted with from (i) 1-3 substituents independently selected from C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, R^d or R^e; or (ii) 1, 2 or 3 R^a substituents; or (iii) 1, 2 or 3 R^b substituents; or (iv) 1, 2 or 3 R^c substituents; or (v) 1, 2 or 3 R^d substituents; or (vi) 1, 2 or 3 R^f groups; the subscript n is 1, 2, 3, 4 or 5 and the subscript m is 0, 1, 2 or 3. In other embodiments, R^{11} is C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or R^e. In some embodiments, R^{11} is halogen, C_{1-6}alkyoxycarbonyl, C_{1-6}alkyl, C_{1-6}alkyl-(CO)NH- or C_{1-6}alkyl-(CO)(C_{1-6}alkyl)N-. In certain embodiments, R^{11} is methoxycarbonyl, ethoxycarbonyl, -CH_3, CH_3(CO)NH-, vinyl, propen-3-yl or CH_3(CO)(CH_3)N-. In one embodiment of compounds of formula Ig-2, the subscript n is 1, m is 0 or 1. In another embodiment of compounds of formula Ig-2, the subscript n is 2, m is 0, 1 or 2. In yet another embodiment, of compounds of formula Ig-2, the subscript n is 3, m is 0, 1 or 2. All the other variables are as defined in any of the embodiments described herein.

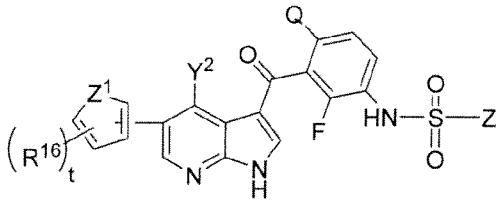
[0111] In a thirteenth embodiment of the invention, compounds of formula (I) have subformula (Ig-3):



Ig-3

All the variables R^{15}, Y^2, Q, R^7 and R^8 are as defined in any of the embodiments described herein. In a preferred embodiment, Y^2 is H. In some embodiments, R^{15} is H or R^1. In some embodiments, R^{15} is R^a, R^b, R^c, R^d or R^e. In one embodiment, R^{15} is C_{1-6}alkyl. In another embodiment, R^{15} is C_{3-6}cycloalkyl. In yet another embodiment, R^{15} is heterocycloalkyl. In some embodiments, R^7 and R^8 are each independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or -X^2R^9, wherein the aliphatic or aromatic portion of R^7 and R^8 are each optionally substituted with from 1 to 3 members independently selected from the group consisting of C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and R^e, provided at each occurrence, at least two of the R^6, R^7 and R^8 groups are not simultaneously hydrogen; and wherein X^2 is –NR^{10}, O or S; R^{10} is H, C_{1-6}alkyl or aryl; and R^9 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, wherein R^9 is optionally substituted with from 1 to 3 R^e substituents. In certain instances, -C(R^7)(R^8) is a branched C_{3-6}alkyl. In one embodiment, -C(R^7)(R^8) is isopropyl. In another embodiment, -C(R^7)(R^8) is sec-butyl. In yet another embodiment, -C(R^7)(R^8) is pentan-2-yl. In still another embodiment, -C(R^7)(R^8) is pentan-3-yl. All the other variables are as defined in any of the embodiments described herein.

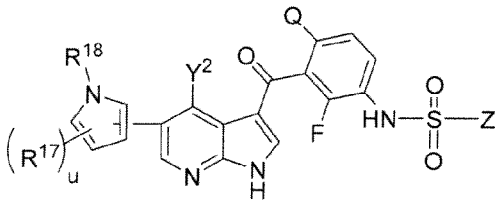
[0112] In a fourteenth embodiment of the invention, compounds of formula (I) have subformula (Ih):



Ih

wherein Z^1 is O or S; R^{16} is H or R^1; or two adjacent R^{16} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; where the 5 to 6-membered-ring is optionally substituted with from 1 to 3 R^d or R^e substituents; and the subscript t is an integer of 1 to 3. In one embodiment, Z^1 is O. In another embodiment, Z^1 is S. In one embodiment, t is 1. In another embodiment, t is 2. In yet another embodiment, t is 3 and two adjacent R^{16} substituents together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; wherein the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents, and the other R^{16} is H, R^d or R^e. In some embodiments, the two adjacent R^{16} together with the atoms to which they are attached form an optionally substituted fused carbocyclic ring, including, but not limiting to, benzene, cyclopentane and cyclohexane rings. The substituents on the carbocyclic ring can be from 1-2 R^d or R^e groups. In other embodiments, two adjacent R^{16} groups together with the atoms to which they are attached form an optionally substituted fused heterocyclic ring, including, but not limiting to, pyrrole, furan, thiophene, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyridine, pyrazine, pyridazine, tetrahydrfuran, tetrahydropyran, tetrahydrothiophene, pyrazolidine, isoxazolidine, imidazolidine, oxazolidine, thiazolidine, isothiazolidine, piperidine, piperazine, and hexahydropyrimidine rings. In other embodiments, R^{16} is halogen, -CN, -OH, $-CF_3$, CF_3O-, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, $-NO_2$, benzyl, phenyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexymethyl, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ or $-NR^bR^b$. In some embodiments, R^{16} is F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl. All the other variables Y^2, Q and Z are as defined in any of the embodiments described herein.

[0113] In a fifteenth embodiment of the invention, compounds of formula (I) have subformula (Ii):

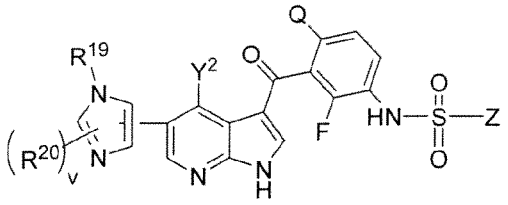


Ii

wherein R^{18} is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl or C_{3-6}cycloalkyl. R^{17} is H or R^1; or two adjacent R^{17} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; or R^{17} and R^{18} taken together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S, where the 5 to 6-membered-ring is optionally substituted with from 1 to 3 R^d or R^e substituents; R^{18} is H, C_{1-6}alkyl or C_{1-6}haloalkyl; and the subscript u is an integer of 1 to 3. In one embodiment, u is 1. In another embodiment, u is 2. In yet another embodiment, u is 3 and two adjacent R^{17} substituents together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; wherein the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents, and the other R^{17} is H, R^d or R^e. In other embodiments, R^{17} and R^{18} taken together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S, where the 5 to 6-membered-ring is optionally substituted with from 1 to 3 R^d or R^e substituents. In some embodiments, (i) the two adjacent R^{17} together with the atoms to which they are attached or (ii) R^{17} and R^{18} taken together with the atoms to which they are attached, form an optionally substituted fused carbocyclic ring, including, but not limiting to, benzene, cyclopentane and cyclohexane rings. The substituents on the carbocyclic ring can be from 1-2 R^d or R^e groups. In other embodiments, (i) two adjacent R^{17} groups together with the atoms to which they are attached or (ii) R^{17} and R^{18} taken together with the atoms to which they are attached, form an optionally substituted fused heterocyclic ring, including, but not limiting to, pyrrole, furan, thiophene, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyridine, pyrazine, pyridazine, tetrahydrfuran, tetrahydropyran, tetrahydrothiophene, pyrazolidine, isoxazolidine, imidazolidine, oxazolidine, thiazolidine, isothiazolidine, piperidine, piperazine, and hexahydropyrimidine rings. In some embodiments, R^{17} is halogen, -CN, -OH, $-CF_3$, CF_3O-, C_{1-6}alkyl, C_{1-6}alkoxy, $-NO_2$, benzyl, phenyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexymethyl, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ or $-NR^bR^b$. In some embodiments, R^{17} is F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl. In certain instances, R^{18} is H, C_{1-6}alkyl or C_{1-6}haloalkyl. In some embodiments, R^{18} is H, C_{1-6}alkyl or cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, or cyclohexylmethyl. In some

embodiments, R^{18} is H or CH_3. All the other variables Y^2, Q and Z are as defined in any of the embodiments described herein.

[0114] In a sixteenth embodiment of the invention, compounds of formula (I) have subformula (Ij):

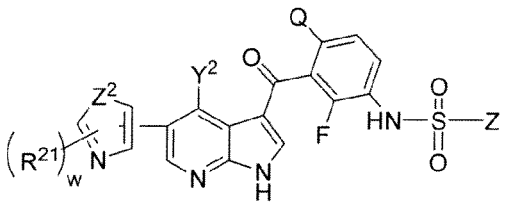


Ij

R^{19} is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl or C_{3-6}cycloalkyl. R^{20} is H or R^1; or two adjacent R^{20} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; or R^{20} and R^{19} taken together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; R^{19} is H, C_{1-6}alkyl or C_{1-6}haloalkyl; and the subscript v is an integer of 1 or 2, where the 5 to 6-membered-ring is optionally substituted with from 1 to 3 R^d or R^e substituents. In one embodiment, v is 1. In some embodiments, two adjacent R^{20} substituents together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; wherein the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents. In other embodiments, v is 2, R^{19} and R^{20} taken together with the atoms to which they are attached form a 5 to 6-membered ring having from 0-2 heteroatoms as ring members selected from O, N or S, where the 5 to 6-membered-ring is optionally substituted with from 1 to 3 R^d or R^e substituents, and the other R^{20} is H, R^d or R^e. In some embodiments, (i) the two adjacent R^{20} together with the atoms to which they are attached or (ii) R^{19} and R^{20} taken together with the atoms to which they are attached, form an optionally substituted fused carbocyclic ring, including, but not limiting to, cyclopentane, cyclohexane and benzene rings. The substituents on the carbocyclic ring can be from 1-2 R^d or R^e groups. In other embodiments, (i) two adjacent R^{19} groups together with the atoms to which they are attached or (ii) R^{19} and R^{20} taken together with the atoms to which they are attached, form an optionally substituted fused heterocyclic ring, including, but not limiting to, pyrrole, furan, thiophene, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyridine, pyrazine, pyridazine, tetrahydrfuran, tetrahydropyran, tetrahydrothiophene, pyrazolidine, isoxazolidine, imidazolidine, oxazolidine, thiazolidine, isothiazolidine, piperidine, piperazine, and hexahydropyrimidine rings. In other embodiments, R^{20} is halogen, -CN, -OH, $-CF_3$, CF_3O-, C_{1-6}alkyl, C_{1-6}alkoxy, $-NO_2$, benzyl, phenyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexymethyl, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ or $-NR^bR^b$. In some embodiments, R^{20} is F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl,

2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl. In certain instances, R^{19} is H, C_{1-6}alkyl or C_{1-6}haloalkyl. In some embodiments, R^{19} is H, C_{1-6}alkyl or cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, or cyclohexylmethyl. In some embodiments, R^{19} is H or CH_3. All the other variables Y^2, Q and Z are as defined in any of the embodiments described herein.

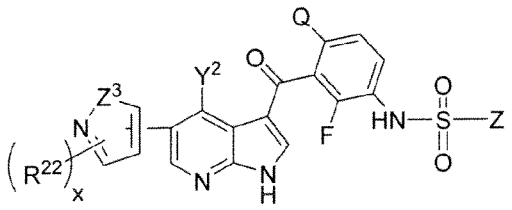
[0115] In a seventeenth embodiment of the invention, compounds of formula (I) have subformula (Ik):



Ik

Z^2 is O or S. The subscript w is 1 or 2. R^{21} is H or R^1; or two adjacent R^{21} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S, where the 5 to 6-membered-ring is optionally substituted with from 1 to 3 R^d or R^e substituents. In one embodiment, w is 1. In another embodiment, w is 2. In some embodiments, two adjacent R^{21} substituents together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; wherein the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents. In some embodiments, the two adjacent R^{21} together with the atoms to which they are attached form an optionally substituted fused carbocyclic ring, including, but not limiting to, cyclopentane, cyclohexane and benzene rings. In certain instances, the substituents on the carbocyclic ring can be from 1-2 R^d or R^e groups. In other embodiments, two adjacent R^{21} groups together with the atoms to which they are attachedform an optionally substituted fused heterocyclic ring, including, but not limiting to, pyrrole, furan, thiophene, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyridine, pyrazine, pyridazine, tetrahydrfuran, tetrahydropyran, tetrahydrothiophene, pyrazolidine, isoxazolidine, imidazolidine, oxazolidine, thiazolidine, isothiazolidine, piperidine, piperazine, and hexahydropyrimidine rings. In certain instances, the substituents on the heterocyclic ring can be from 1-2 R^d or R^e groups. In other embodiments, R^{21} is halogen, -CN, -OH, $-CF_3$, CF_3O-, C_{1-6}alkyl, C_{1-6}alkoxy, $-NO_2$, benzyl, phenyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexymethyl, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ or $-NR^bR^b$. In some embodiments, R^{21} is F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl. All the other variables Y^2, Q and Z are as defined in any of the embodiments described herein.

[0116] In an eighteenth embodiment of the invention, compounds of formula (I) have subformula (II):

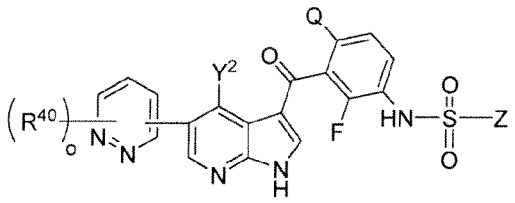


II

Z^3 is O, S or $-N(R^{30})$, where R^{30} is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl or C_{3-6}cycloalkyl. The subscript x is 1 or 2. R^{22} is H or R^1; or two adjacent R^{22} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S, where the 5 to 6-membered-ring is optionally substituted with from 1 to 3 R^d or R^e substituents. In one embodiment, x is 1. In another embodiment, x is 2. In some embodiments, two adjacent R^{22} substituents together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; wherein the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents. In other embodiments, x is 2, R^{22} and R^{30} taken together with the atoms to which they are attached form a 5 to 6-membered ring having from 0-2 heteroatoms as ring members selected from O, N or S, where the 5 to 6-membered-ring is optionally substituted with from 1 to 3 R^d or R^e substituents. In some embodiments, (i) the two adjacent R^{22} together with the atoms to which they are attached or (ii) R^{22} and R^{30} taken together with the atoms to which they are attached, form an optionally substituted fused carbocyclic ring, including, but not limiting to, cyclopentane, cyclohexane and benzene rings. In certain instances, the substituents on the carbocyclic ring can be from 1-2 R^d or R^e groups. In other embodiments, (i) two adjacent R^{22} groups together with the atoms to which they are attached or (ii) R^{22} and R^{30} taken together with the atoms to which they are attached, form an optionally substituted fused heterocyclic ring, including, but not limiting to, pyrrole, furan, thiophene, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyridine, pyrazine, pyridazine, tetrahydrfuran, tetrahydropyran, tetrahydrothiophene, pyrazolidine, isoxazolidine, imidazolidine, oxazolidine, thiazolidine, isothiazolidine, piperidine, piperazine, and hexahydropyrimidine rings. In other embodiments, R^{22} is halogen, -CN, -OH, $-CF_3$, CF_3O-, C_{1-6}alkyl, C_{1-6}alkoxy, $-NO_2$, benzyl, phenyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexymethyl, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ or $-NR^bR^b$. In some embodiments, R^{22} is F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl. In certain instances, R^{30} is H, C_{1-6}alkyl or C_{1-6}haloalkyl. In some embodiments, R^{30} is H, C_{1-6}alkyl or cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl,

cyclohexyl, or cyclohexylmethyl. In some embodiments, R^{30} is H or CH_3. All the other variables Y^2, Q and Z are as defined in any of the embodiments described herein.

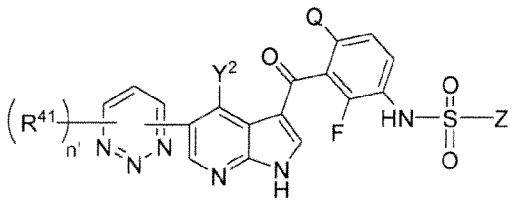
[0117] In a nineteenth embodiment of the invention, compounds of formula (I) have subformula (Im):



Im

R^{40} is H or R^1; or two adjacent R^{40} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; and the subscript o is an integer of 1 to 3, where the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents. In one embodiment, the subscript o is 1. In another embodiment, the subscriot o is 2. In yet another embodiment, the subscript o is 3 and two adjacent R^{40} substituents together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; wherein the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents, and the other R^{40} is H, R^d, R^e or R^f. In some embodiments, the two adjacent R^{40} together with the atoms to which they are attached form an optionally substituted fused carbocyclic ring, including, but not limiting to, benzene, cyclopentane and cyclohexane rings. The substituents on the carbocyclic ring can be from 1-2 R^d or R^e groups. In other embodiments, two adjacent R^{40} groups together with the atoms to which they are attached form an optionally substituted fused heterocyclic ring, including, but not limiting to, pyrrole, furan, thiophene, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyridine, pyrazine, pyridazine, tetrahydrfuran, tetrahydropyran, tetrahydrothiophene, pyrazolidine, , isoxazolidine, imidazolidine, oxazolidine, thiazolidine, isothiazolidine, piperidine, piperazine, and hexahydropyrimidine rings. In other embodiments, R^{40} is halogen, -CN, -OH, $-CF_3$, CF_3O-, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, $-NO_2$, benzyl, phenyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexymethyl, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ or $-NR^bR^b$. In some embodiments, R^{40} is F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido or methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl. All the other variables Y^2, Q and Z are as defined in any of the embodiments described herein.

[0118] In a twentieth embodiment of the invention, compounds of formula (I) have subformula (In):



In

R^{41} is H or R^1; or two adjacent R^{41} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; and the subscript n' is an integer of 1 or 2, where the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents. In one embodiment, the subscript n' is 1. In another embodiment, the subscriot n' is 2. In some embodiments, the two adjacent R^{41} substituents together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; wherein the 5 to 6-membered-ring is optionally substituted with from 1-3 R^d or R^e substituents. In some embodiments, the two adjacent R^{41} together with the atoms to which they are attached form an optionally substituted fused carbocyclic ring, including, but not limiting to, benzene, cyclopentane and cyclohexane rings. The substituents on the carbocyclic ring can be from 1-2 R^d or R^e groups. In other embodiments, two adjacent R^{41} groups together with the atoms to which they are attached form an optionally substituted fused heterocyclic ring, including, but not limiting to, pyrrole, furan, thiophene, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyridine, pyrazine, pyridazine, tetrahydrfuran, tetrahydropyran, tetrahydrothiophene, pyrazolidine, , isoxazolidine, imidazolidine, oxazolidine, thiazolidine, isothiazolidine, piperidine, piperazine, and hexahydropyrimidine rings. In other embodiments, R^{41} is halogen, -CN, -OH, $-CF_3$, CF_3O-, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, $-NO_2$, benzyl, phenyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexymethyl, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ or $-NR^bR^b$. In some embodiments, R^{41} is F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido or methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl. All the other variables Y^2, Q and Z are as defined in any of the embodiments described herein.

[0119] In some embodiments, the invention provides a compound selected from the group consisting of:

N-[3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0012)**;

5-chloro-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0013)**;

5-(4-chlorophenyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0014)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0015)**;

N-[2,4-difluoro-3-(5-fluoro-4-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide **(P-0016)**;

N-[3-[4-(cyclopropylmethylamino)-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0017)**;

5-cyano-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0018)**;

5-chloro-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0019)**;

5-(4-chlorophenyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0020)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0021)**;

N-[3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0022)**;

N-[3-[5-[2-(dimethylamino)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0023)**;

N-[2-fluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide **(P-0024)**;

N-[2,4-difluoro-3-(5-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide **(P-0025)**;

3-[3-[[cyclopropyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0026)**;

[2-fluoro-3-(methylsulfamoylamino)phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone **(P-0027)**;

5-(4-cyanophenyl)-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0028)**;

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine **(P-0029)**;

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-(6-methyl-3-pyridyl)-1H-pyrrolo[2,3-b]pyridine **(P-0030)**;

5-[6-(dimethylamino)-3-pyridyl]-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0031)**;

5-(4-cyanophenyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0032)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine **(P-0033)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(6-methyl-3-pyridyl)-1H-pyrrolo[2,3-b]pyridine **(P-0034)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine **(P-0035)**;

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-phenyl-1H-pyrrolo[2,3-b]pyridine **(P-0036)**;

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-phenyl-1H-pyrrolo[2,3-b]pyridine **(P-0037)**;

5-bromo-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0038)**;

5-cyano-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0039)**;

3-[2-fluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0040)**;

3-benzyloxy-N-[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0041)**;

1-cyclopropyl-N-[2-fluoro-3-[5-(1-methylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]methanesulfonamide **(P-0042)**;

N-[2-fluoro-3-[5-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0043)**;

N-[3-[5-(2,4-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0044)**;

N-[2-fluoro-3-[5-(6-methyl-3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0045)**;

N-[3-[5-[6-(dimethylamino)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0046)**;

N-[2-fluoro-3-[5-(2-isopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0047)**;

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0048)**;

N-[3-[5-(4-cyano-3-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0049)**;

N-[3-[5-[4-(1-cyanocyclopropyl)phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0050)**;

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-(2-isopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0051)**;

5-(2-cyclopropylpyrimidin-5-yl)-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0052)**;

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-[6-(trifluoromethyl)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine **(P-0053)**;

5-(4-cyano-3-methoxy-phenyl)-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0054)**;

5-[4-(1-cyanocyclopropyl)phenyl]-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0055)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0056)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-isopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0057)**;

5-(2-cyclopropylpyrimidin-5-yl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0058)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-[6-(trifluoromethyl)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine **(P-0059)**;

5-(4-cyano-3-methoxy-phenyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0060)**;

5-[4-(1-cyanocyclopropyl)phenyl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0061)**;

N-[2-fluoro-3-[5-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0062)**;

N-[2-fluoro-3-(5-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide **(P-0063)**;

5-[2-(cyclopropylamino)pyrimidin-5-yl]-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0064)**;

N-[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]-2-methoxy-ethanesulfonamide **(P-0065)**;

methyl 3-[[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]sulfamoyl]propanoate **(P-0066)**;

N-[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]cyclopropanesulfonamide **(P-0067)**;

[3-(ethylsulfamoylamino)-2-fluoro-phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone **(P-0068)**;

[3-(ethylsulfamoylamino)-2-fluoro-phenyl]-(5-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone **(P-0069)**;

3-[2-fluoro-3-[[isobutyl(methyl)sulfamoyl]amino]benzoyl]-5-iodo-1H-pyrrolo[2,3-b]pyridine **(P-0070)**;

[2-fluoro-3-(isopropylsulfamoylamino)phenyl]-(5-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone **(P-0071)**;

3-[2-fluoro-3-[[isobutyl(methyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0072)**;

3-[2-fluoro-3-[[2-methoxyethyl(methyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0073)**;

N-[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]-2-methyl-pyrrolidine-1-sulfonamide **(P-0074)**;

3-[2-fluoro-3-[[isopropyl(methyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0075)**;

5-[6-(dimethylamino)-3-pyridyl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0076)**;

5-[2-(cyclopropylamino)pyrimidin-5-yl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0077)**;

5-(2-cyclopropylpyrimidin-5-yl)-3-[2,6-difluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0078)**;

5-[4-(1-cyanocyclopropyl)phenyl]-3-[2,6-difluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0079)**;

5-[4-(1-cyanocyclopropyl)phenyl]-3-[2-fluoro-3-[[2-methoxyethyl(methyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0080)**;

5-[2-(cyclopropylamino)pyrimidin-5-yl]-3-[2-fluoro-3-[[2-methoxyethyl(methyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0081)**;

5-[2-(cyclopropylamino)pyrimidin-5-yl]-3-[2-fluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0082)**;

3-[3-[[cyclopropylmethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0083)**;

3-[3-[[cyclopropylmethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0084)**;

5-(2-cyclopropylpyrimidin-5-yl)-3-[2-fluoro-3-[[2-methoxyethyl(methyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0085)**;

5-(2-cyclopropylpyrimidin-5-yl)-3-[2-fluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0086)**;

5-(6-cyclopropyl-3-pyridyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0087)**;

3,3-difluoro-N-[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]azetidine-1-sulfonamide **(P-0088)**;

4-[[(1S)-1-cyclopropylethyl]amino]-5-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-7H-pyrrolo[2,3-d]pyrimidine **(P-0089)**;

N-[3-[5-(4-cyanophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0090)**;

N-[3-[5-(2-cyanopyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0091)**;

N-[2-fluoro-3-[5-(2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0092)**;

N-[3-[5-(5-cyano-3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0093)**;

N-[2-fluoro-3-[5-[6-(trifluoromethyl)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0095)**;

5-(2-cyanopyrimidin-5-yl)-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0096)**;

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-(2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0097)**;

5-(5-cyano-3-pyridyl)-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0098)**;

5-(6-cyano-3-pyridyl)-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0099)**;

5-(2-cyanopyrimidin-5-yl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0100)**;

5-(5-cyano-3-pyridyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0101)**;

5-(6-cyano-3-pyridyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0102)**;

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-[4-(1-hydroxy-1-methyl-ethyl)phenyl]-1H-pyrrolo[2,3-b]pyridine **(P-0103)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-[4-(1-hydroxy-1-methyl-ethyl)phenyl]-1H-pyrrolo[2,3-b]pyridine **(P-0104)**;

N-[2-fluoro-3-[5-[4-(1-hydroxy-1-methyl-ethyl)phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0105)**;

5-[2-(dimethylamino)pyrimidin-5-yl]-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0106)**;

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0107)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0108)**;

N-[2-fluoro-3-[5-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0109)**;

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-iodo-1H-pyrrolo[2,3-b]pyridine **(P-0110)**;

3-[2-fluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-5-(2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0111)**;

3-[3-[[cyclopropylmethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0112)**;

5-(6-cyclopropyl-3-pyridyl)-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0113)**;

5-(6-cyclopropyl-3-pyridyl)-3-[2-fluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0114)**;

3-[3-[[cyclopropylmethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(6-cyclopropyl-3-pyridyl)-1H-pyrrolo[2,3-b]pyridine **(P-0115)**;

3-[2,6-difluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0116)**;

[2-fluoro-3-(propylsulfamoylamino)phenyl]-(5-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone **(P-0117)**;

[2-fluoro-3-(propylsulfamoylamino)phenyl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone **(P-0223)**;

N-[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]butane-2-sulfonamide **(P-0024)**;

N-[2-fluoro-3-[5-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]butane-2-sulfonamide **(P-0225)**;

N-[3-[5-[2-(cyclopropylamino)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]butane-2-sulfonamide **(P-0226)**;

N-[3-[5-[4-(1-cyanocyclopropyl)phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]butane-2-sulfonamide **(P-00227)**;

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]butane-2-sulfonamide **(P-0228)**;

N-[2-fluoro-3-[5-(2-isopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]butane-2-sulfonamide **(P-0229)**;

N-[3-[5-[6-(dimethylamino)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]butane-2-sulfonamide **(P-0230)**;

N-[2-fluoro-3-[5-(2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]butane-2-sulfonamide **(P-0231)**;

N-[3-[5-[2-(cyclopropylamino)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0232)**;

5-(2-cyclopropylpyrimidin-5-yl)-3-[2-fluoro-3-[[isopropyl(methyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0233)**;

N-[2-fluoro-3-[5-(2-morpholinopyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide; (**P-0235**);

N-[2-fluoro-3-[5-(2-morpholinopyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]butane-2-sulfonamide (**P-0236**);

5-[4-(1-cyanocyclopropyl)phenyl]-3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0237**);

5-(2-cyclopropylpyrimidin-5-yl)-3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0238**);

5-[4-(1-cyanocyclopropyl)phenyl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0239**);

5-(2-cyclopropylpyrimidin-5-yl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0240**);

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide (**P-0241**);

[2-fluoro-3-(propylsulfamoylamino)phenyl]-[5-(1-methylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (**P-0242**);

1-[4-[3-[2-fluoro-3-(pyrrolidin-1-ylsulfonylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]cyclopropanecarboxylic acid (**P-0243**);

3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-5-(5-ethoxypyrazin-2-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0244**);

5-[4-(1-cyano-1-methyl-ethyl)phenyl]-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0245**);

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]-3,3-dimethyl-pyrrolidine-1-sulfonamide (**P-0246**);

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]-3-methyl-pyrrolidine-1-sulfonamide (**P-0247**);

N-[3-[5-[4-(1-cyanocyclopropyl)phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide (**P-0248**);

3-[3-[[cyclopropyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0249**);

[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-[2-fluoro-3-(propylsulfamoylamino)phenyl]methanone (**P-0251**);

3-[3-[[cyclopropyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0252**);

1-[4-[3-[2-fluoro-3-(pyrrolidin-1-ylsulfonylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]cyclopropanecarboxamide (**P-0253**);

methyl 1-[4-[3-[2-fluoro-3-(pyrrolidin-1-ylsulfonylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]cyclopropanecarboxylate **(P-0254)**;

5-[4-(1-cyano-1-methyl-ethyl)phenyl]-3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0255)**;

5-(2-ethoxypyrimidin-5-yl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0256)**;

ethyl 1-[[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]sulfamoyl]pyrrolidine-2-carboxylate **(P-0257)**;

4-[5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyrimidin-2-yl]morpholine **(P-0258)**;

4-[3-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]morpholine **(P-0259)**;

N-[2,4-difluoro-3-[5-[2-(4-methylpiperazin-1-yl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0260)**;

N-[2,4-difluoro-3-[5-(2-piperazin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0261)**;

N-[2,4-difluoro-3-[5-[2-(4-hydroxy-1-piperidyl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0262)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-[2-(4-methylpiperazin-1-yl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine **(P-0263)**;

tert-butyl 4-[5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyrimidin-2-yl]piperazine-1-carboxylate **(P-0264)**;

N-[2,4-difluoro-3-[5-[2-(1-hydroxy-1-methyl-ethyl)thiazol-4-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0265)**;

N-[2,4-difluoro-3-[5-(2-morpholinopyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0266)**;

N-[1-[[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]sulfamoyl]pyrrolidin-3-yl]-N-methyl-acetamide **(P-0267)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(2-piperazin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0268)**;

N-[3-[5-[2-(azetidin-1-yl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0269)**;

N-[2,4-difluoro-3-[5-(2-methoxythiazol-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0270)**;

(3R)-N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]-3-methyl-pyrrolidine-1-sulfonamide **(P-0271)**;

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]-3-(methylamino)pyrrolidine-1-sulfonamide **(P-0272)**;

N-[2,4-difluoro-3-[5-(4-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0273)**;

N-[3-(5-cyclopropyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0274)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-[2-(4-hydroxy-1-piperidyl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine **(P-0275)**;

5-[3-(1-cyanocyclopropyl)phenyl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0276)**;

5-[2-(azetidin-1-yl)pyrimidin-5-yl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0277)**;

N-[3-[5-(2-aminopyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0279)**;

N-[3-[5-(2-aminopyrimidin-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0280)**;

N-[2-fluoro-3-[5-(4-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0281)**;

N-[2,4-difluoro-3-[5-(2-morpholinopyrimidin-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0282)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(2-fluoro-4-pyridyl)-1H-pyrrolo[2,3-b]pyridine **(P-0283)**;

N-[2,4-difluoro-3-[5-(2-morpholino-4-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0284)**;

N-[2,4-difluoro-3-[5-[2-(4-methylpiperazin-1-yl)-4-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0285)**;

N-[3-[5-[2-(cyclobutoxy)-4-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0286)**;

N-[2,4-difluoro-3-[5-(2-methoxy-4-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0287)**;

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]-3,3-difluoro-pyrrolidine-1-sulfonamide **(P-0288)**;

(3S)-N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]-3-fluoro-pyrrolidine-1-sulfonamide **(P-0289)**;

methyl 2-[[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]sulfamoyl]propanoate **(P-0291)**;

5-[2-(dimethylamino)pyrimidin-5-yl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0292)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0293)**;

N-[2,4-difluoro-3-[5-[6-(trifluoromethyl)pyrimidin-4-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0294)**;

N-[3-[5-(2-cyclopropyl-4-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0295)**;

5-cyclobutyl-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0297)**;

5-cyclopropyl-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0298)**;

N-[3-[5-(6-aminopyrimidin-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0299)**;

5-(4-cyanophenyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0300)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-[4-(trifluoromethyl)phenyl]-1H-pyrrolo[2,3-b]pyridine **(P-0301)**;

5-[3-(dimethylamino)phenyl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0302)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(4-pyrrolidin-1-ylphenyl)-1H-pyrrolo[2,3-b]pyridine **(P-0303)**;

2-[4-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]-5-methyl-1,3,4-oxadiazole **(P-0304)**;

2-[4-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]-5-(methylamino)-1,3,4-thiadiazole **(P-0305)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-[5-(1-hydroxy-1-methyl-ethyl)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine **(P-0306)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-[6-(1-hydroxy-1-methyl-ethyl)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine **(P-0307)**;

5-[4-(diethylamino)phenyl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0308)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(2-oxoindolin-6-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0309)**;

3-[5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-thienyl]-5-methyl-1,2,4-oxadiazole **(P-0310)**;

2-amino-6-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]quinazoline **(P-0311)**;

N-cyclopropyl-5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide **(P-0312)**;

2-(dimethylamino)-6-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]quinazoline **(P-0313)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-[4-(1-hydroxycyclopropyl)phenyl]-1H-pyrrolo[2,3-b]pyridine **(P-0314)**;

5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]thiazole **(P-0315)**;

4-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-(1-hydroxy-1-methyl-ethyl)thiazole **(P-0316)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(6-methoxypyridazin-3-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0317)**;

N-[2,4-difluoro-3-[5-(6-morpholinopyrimidin-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0318)**;

N-[2,4-difluoro-3-[5-[6-(4-methylpiperazin-1-yl)pyrimidin-4-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0319)**;

(3S)-N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]-3-methyl-pyrrolidine-1-sulfonamide **(P-0320)**;

N-[2-fluoro-3-[5-(6-morpholinopyrimidin-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0321)**;

N-[2-fluoro-3-[5-[6-(4-methylpiperazin-1-yl)pyrimidin-4-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0322)**;

N-[2-fluoro-3-[5-[6-(4-methylpiperazin-1-yl)-2-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0324)**;

N-[2-fluoro-3-[5-(4-methoxypyrimidin-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0325)**;

N-[2-fluoro-3-[5-(4-methylpyrimidin-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0326)**;

(3R)-N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]-3-fluoro-pyrrolidine-1-sulfonamide **(P-0327)**;

[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-[2,6-difluoro-3-(methylsulfamoylamino)phenyl]methanone **(P-0334)**;

[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-[3-(ethylsulfamoylamino)-2,6-difluoro-phenyl]methanone **(P-0335)**;

5-(2-cyclopropylpyrimidin-5-yl)-3-[2,6-difluoro-3-(sulfamoylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0336)**;

N-[3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]butane-2-sulfonamide **(P-0337)**;

(3R)-N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]-3-fluoro-pyrrolidine-1-sulfonamide **(P-0338)**;

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]-3-fluoro-pyrrolidine-1-sulfonamide **(P-0339)**;

5-(2-cyclopropylpyrimidin-5-yl)-3-[2,6-difluoro-3-[[methyl(2,2,2-trifluoroethyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0340)**;

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]butane-2-sulfonamide **(P-0342)**;

5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-methoxy-thiazole **(P-0343)**;

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0344)**;

N-[2,4-difluoro-3-[5-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0345)**;

N-[3-(5-cyclobutyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0346)**;

N-[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]cyclopropanesulfonamide **(P-0347)**;

1-allyl-N-[3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]cyclopropanesulfonamide **(P-0348)**;

N-[2,4-difluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]cyclopropanesulfonamide **(P-0349)**;

N-[2,4-difluoro-3-[5-(5-methoxy-3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]cyclopropanesulfonamide **(P-0350)**; and

N-[3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]cyclopropanesulfonamide **(P-0351)**;

or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof. In some embodiments, the invention provides the above selected compounds and pharmaceutically acceptable salts thereof. In other embodiments, the invention provides the above selected compounds and pharmaceutically acceptable salts and tautomers and isomers thereof.

[0120] In other embodiments, the invention provides a compound selected from any of P-0108 to P-0222 as set forth in Table 3 and pharmaceutically acceptable salts, hydrates, solvates, tautomers and isomers thereof. In some embodiments, the invention provides any of the above selected compounds and pharmaceutically acceptable salts thereof. In some embodiments, the invention provides any of the above selected compounds and pharmaceutically acceptable salts and tautomers and isomers thereof.

[0121] In some embodiments, when Y^1 is optionally substituted 2-pyridyl, 3-pyridyl or 4-pyridyl, Z is other than $-N(CH_3)(CH_3)$ or $-N(R^4)_2$, wherein R^4 is C_{1-6}alkyl. In some embodiments, when Y^1 is phenyl, Z is other than $-N(CH_3)(CH_3)$ or $-N(R^4)_2$, wherein R^4 is C_{1-6}alkyl. In other embodiments, when Y^1 is halogen, Z is other than $-N(CH_3)(CH_3)$, $-N(Et)_2$, 1-pyrrolinyl, 1-piperidinyl, 4-

morpholinyl or $-N(R^4)_2$, wherein R^4 is C_{1-6}alkyl. In some embodiments, when Y^1 is CH_3 or C_{1-6}alkyl, Z is other than $-N(CH_3)(CH_3)$, $-N(Et)_2$, 1-pyrrolinyl, 1-piperridinyl, 4-morpholinyl or $-N(R^4)_2$, wherein R^4 is C_{1-6}alkyl. In some embodiments, when Y^1 is CH_3O- or C_{1-6}alkoxy, Z is other than $-N(CH_3)(CH_3)$, $-N(Et)_2$, 1-pyrrolinyl, 1-piperridinyl, 4-morpholinyl or $-N(R^4)_2$, wherein R^4 is C_{1-6}alkyl. In some embodiments, when Y^1 is CN, Z is other than $-N(CH_3)(CH_3)$, $-N(Et)_2$, 1-pyrrolinyl, 1-piperridinyl, 4-morpholinyl or $-N(R^4)_2$, wherein R^4 is C_{1-6}alkyl. In certain instances, when Y^1 is halogen, $-CH_3$, -CN, -OMe or 2-methoxypyrimidin-5-yl, Z is other than C_{3-6}cycloalkyl. In other instances, when Y^1 is 1-methyl-4-pyrazolyl, 3-methylsulfonylphenyl or 3-methylsulfonylaminophenyl, Z is other than C_{3-6}cycloalkyl. In other instances, when Y^1 is C_{1-6}alkyl or C_{1-6}alkoxy, Z is other than C_{3-6}cycloalkyl. In other instances, when Y^1 is 1-C_{1-6}alkyl-4-pyrazolyl, Z is other than cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In other instances, when Y^1 is 1-C_{1-6}alkyl-4-pyrazolyl, Z is other than C_{3-6}cycloalkyl. In other instances, when Y^1 is methylsulfonylphenyl or methylsulfonylaminophenyl, Z is other than cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In other instances, when Y^1 is methylsulfonylphenyl or methylsulfonylaminophenyl, Z is other than C_{3-6}cycloalkyl. In some instances, when Y^1 is 3-C_{1-6}alkylsulfonylphenyl or 3-C_{1-6}alkylsulfonylaminophenyl, Z is other than cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In other instances, when Y^1 is 3-C_{1-6}alkylsulfonylphenyl or 3-C_{1-6}alkylsulfonylaminophenyl, Z is other than C_{3-6}cycloalkyl.

[0122] The following compounds in Table 1 are excluded from the generic formulas I and Ia to In:

Table 1

3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-5-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine;

5-bromo-3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine;

3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-5-phenyl-1H-pyrrolo[2,3-b]pyridine;

N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]piperidine-1-sulfonamide;

5-(4-chlorophenyl)-3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine;

5-chloro-3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine;

(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[3-[dimethylsulfamoyl(methyl)amino]-2,6-difluoro-phenyl]methanone;

N-[2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide;

N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide;

N-[2,4-difluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide;

N-[3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide;

5-cyano-3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine;

3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-5-methyl-1H-pyrrolo[2,3-b]pyridine;

5-chloro-3-[3-(diethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine;

5-cyano-3-[3-(diethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine;

3-[3-(diethylsulfamoylamino)-2,6-difluoro-benzoyl]-5-methyl-1H-pyrrolo[2,3-b]pyridine;

3-[3-(diethylsulfamoylamino)-2,6-difluoro-benzoyl]-5-methoxy-1H-pyrrolo[2,3-b]pyridine;

N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]morpholine-4-sulfonamide;

N-[2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]morpholine-4-sulfonamide;

N-[2,4-difluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]morpholine-4-sulfonamide;

N-[3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]morpholine-4-sulfonamide;

3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine;

N-[2,4-difluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide;

3-[3-(diethylsulfamoylamino)-2,6-difluoro-benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine;

N-[2,4-difluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]morpholine-4-sulfonamide;

5-cyano-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine;

N-[3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]pyrrolidine-1-sulfonamide;

N-[3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]morpholine-4-sulfonamide;

N-[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide;

5-(4-chlorophenyl)-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine;

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine;

Propane-2-sulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Pyrrolidine-1-sulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Propane-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

Propane-2-sulfonic acid [3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

Propane-2-sulfonic acid {2,4-difluoro-3-[5-(2-methoxy-pyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide;

Butane-2-sulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Pentane-2-sulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Butane-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

Pentane-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

Butane-2-sulfonic acid [2,4-difluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Pentane-2-sulfonic acid [3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

Pentane-2-sulfonic acid [2,4-difluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Butane-2-sulfonic acid [3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

Butane-2-sulfonic acid {2,4-difluoro-3-[5-(2-methoxy-pyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide;

Cyclobutanesulfonic acid [3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

Cyclobutanesulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

Cyclohexanesulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Cyclopentanesulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Cyclohexanesulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

Cyclopentanesulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

Cyclopentanesulfonic acid [3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

Cyclohexanesulfonic acid [2,4-difluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Cyclobutanesulfonic acid [2,4-difluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Cyclopentanesulfonic acid [2,4-difluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Cyclohexanesulfonic acid [3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

Cyclohexanesulfonic acid {2,4-difluoro-3-[5-(2-methoxy-pyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide;

Cyclopentanesulfonic acid {2,4-difluoro-3-[5-(2-methoxy-pyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide;

Cyclobutanesulfonic acid {2,4-difluoro-3-[5-(2-methoxy-pyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide;

Pyrrolidine-1-sulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Pyrrolidine-1-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

Pyrrolidine-1-sulfonic acid [2,4-difluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Pyrrolidine-1-sulfonic acid [2,4-difluoro-3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

N,N-dimethylamino-sulfonic acid [2,4-difluoro-3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

N,N-dimethylamino-sulfonic acid [2,4-difluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

N,N-diethylamino-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

N,N-diethylamino-sulfonic acid [3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

N,N-diethylamino-sulfonic acid [2,4-difluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

N,N-diethylamino-sulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Morpholine-4-sulfonic acid [3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

Morpholine-4-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide;

Morpholine-4-sulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Morpholine-4-sulfonic acid [2,4-difluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Propane-2-sulfonic acid [3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide;

Butane-2-sulfonic acid [3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide;

Cyclohexanesulfonic acid [3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide;

Cyclopentanesulfonic acid [3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide;

Cyclobutanesulfonic acid [3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide;

Cyclopropanesulfonic acid {4-fluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide;

Cyclohexanesulfonic acid {4-fluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide;

Cyclopropanesulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-4-fluoro-phenyl]-amide;

Cyclohexanesulfonic acid [4-fluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Cyclohexanesulfonic acid {4-fluoro-3-[5-(3-methanesulfonyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide;

Cyclopentanesulfonic acid {4-fluoro-3-[5-(3-methanesulfonyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide;

Cyclohexanesulfonic acid {4-fluoro-3-[5-(3-methanesulfonylamino-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide;

Cyclopentanesulfonic acid {4-fluoro-3-[5-(3-methanesulfonylamino-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide;

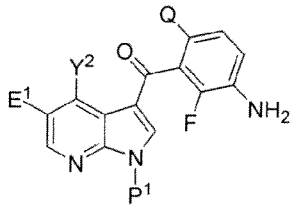
Cyclopentanesulfonic acid [4-fluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide;

Piperidine-1-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-4-fluoro-phenyl]-amide;

N,N-dimethylamino-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide;

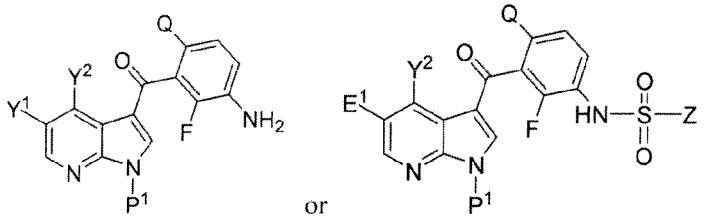
Pyrrolidine-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide.

[0123] In another aspect, the present invention provides a method for preparing a compound of formulas (I) to (In). The method includes contacting a compound having formula II:



II

with an agent selected from Y^1-G^1 (III) or A^1-$S(O)_2$-Z (IV) under conditions sufficient to form a compound having formulas (V) or (VI):

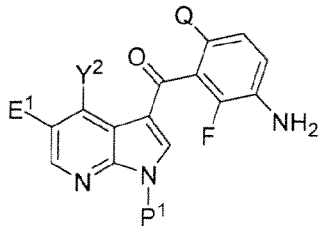


(V) or (VI)

reacting (i) a compound of formula (V) with a compound of formula (IV), or (ii) a compound of formula (VI) with a compound of formula (III) under conditions sufficient to form the compound of formula (I); and wherein E^1 is halogen, tosylate or mesylate; G^1 is $-B(OR^{25})_2$ or $-Sn(Bu)_3$, wherein R^{25} is –OH, alkyl or two $-OR^{25}$ substituents together with the boron atom to which they are attached to form an optionally substituted 5 or 6-membered ring; A^1 is a leaving group, which can be readily displaced by an arylamino group; and P^1 is H or an amino protecting group. In some instances, the substituents for the 5 or 6-membered ring are 1 to 4 members R^e groups. In some embodiments, the reaction of compounds of formula (II) with In one embodiment, E^1 is Cl, Br or I. In another rembodiment, E^1 is tosylate, mesylate or triflate. In one embodiment, G^1 is $-B(OH)_2$. In another embodiment, G^1 is 2-hydroxy-1,3,2-benzodioxaborole or 2-hydroxy-4,4,5,5-tetramethyl-1,3,2-benzodioxaboro. In another embodiment, G^1 is $-Sn(Bu)_3$. In one embodiment, A^1 is Cl or Br. In another embodiment, A^1 is tosylate or mesylate. In one embodiment, P^1 is H. The substituents Y^1, Y^2, Q and Z are as defined in any of formulas (I) to (In) and any of the embodiments disclosed herein.

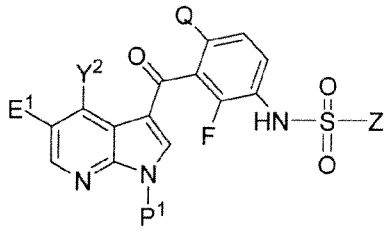
[0124] In some embodiments, the method includes contacting a compound of formula (II) with an agent of formula (III): Y^1-G^1 to form a compound of formula (V), followed by reacting a compound of fomula (V) with an agent of formula (IV): A^1-$S(O)_2$-Z to form a compound of formula (I). In other embodiments, the method includes contacting a compound of formula (II) with an agent of formula (IV): A^1-$S(O)_2$-Z to form a compound of formula (VI), followed by reacting a compound of fomula (VI) with an agent of formula (III): Y^1-G^1 to form a compound of formula (I).

[0125] In yet other embodiments, the invention provides a method for preparing a compound of formulas (I) to (In). The method includes reacting a compound having formula II:



II

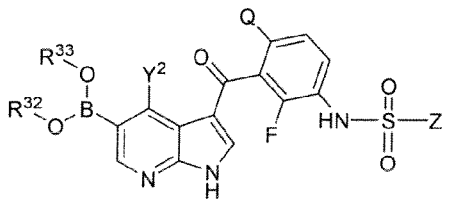
with a compound of formula (IV): A^1-$S(O)_2$-Z under conditions sufficient to form a compound having formula (VI):



(VI)

contacting a compound of formula (VI) with a compound of the formula: Y^1-E^2 and a compound of the formula: $(OR^{31})_2B$-$B(OR^{31})_2$ in the presence of a palladium complex under conditions sufficient to form the compound of formula (I), wherein R^{31} is –OH, alkyl or two $-OR^{31}$ substituents together with the boron atom to which they are attached to form a 5 or 6-membered ring; and wherein E^1 and E^2 are each independently halogen, tosylate or mesylate; A^1 is a leaving group; and P^1 is H or an amino protecting group. Both Pd(0) and Pd(II) complexes can be used. In some embodiments, E^1 is Cl, Br, I, tosylate or mesylate. In some embodiments, E^2 is Cl, Br, I, tosylate or mesylate. In certain instances, the palladium complexes include, but are not limited to, $Pd(PPh_3)_4$, bis(diphenylphosphino)ferrocene]dichloropalladium and the like. The substituents Y^1, Y^2, Q and Z are as defined in any of formulas (I) to (In) and any of the embodiments disclosed herein.

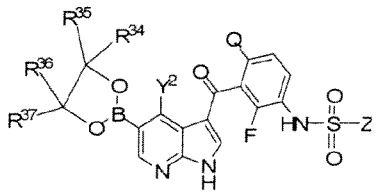
[0126] In another aspect, the invention provides a compound having formula (VIII):



VIII

wherein R^{32} and R^{33} are each independently H, optionally substituted alkyl, optionally substituted arylalkyl or optionally substituted aryl. In ome embodiements, the aryl or alkyl portion of R^{32} or R^{33} is optionally substituted with from 1 to 4 R^e substituents; or R^{32} and R^{33} together with the oxygen atoms to which they are attached form a 5- or 6-membered ring, wherein the 5- or 6-membered ring is optionally substituted with from 1 to 4 R^e groups or fused with an optionally substituted 5- or 6-membered aromatic ring. The substituents Y^2, Q and Z in formula VIII are as defined in in any of formulas (I) to (In) and any of the embodiments as described herein.

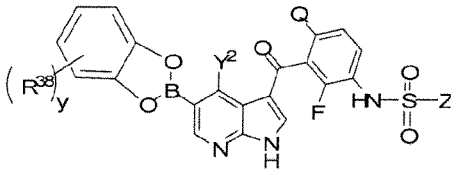
[0127] In some embodiments, the compounds of formula VIII have sub formula VIIIa:



VIIIa

R^{34}, R^{35}, R^{36} and R^{37} are each independently R^e or R^f. In certain instances, R^{34}, R^{35}, R^{36} and R^{37} are each independently C_{1-6} alkyl. In other instances, R^{34}, R^{35}, R^{36} and R^{37} are CH_3. The substituents Y^2, Q and Z in formula VIIIa are as defined in in any of formulas (I) to (In) and any of the embodiments as described herein.

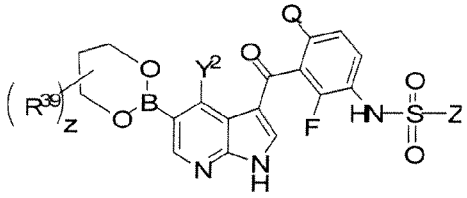
[0128] In some embodiments, the compounds of formula VIII have sub formula VIIIb:



VIIIb

The subscript y is an integer of 1 to 4. Each R^{38} is independently H, R^e or R^f. The substituents Y^2, Q and Z in formula VIIIb are as defined in any of formulas (I) to (In) and any of the embodiments as described herein.

[0129] In some embodiments, the compounds of formula VIII have subformula VIIIc:



VIIIc

The subscript z is an integer of 1 to 4. Each R^{39} is independently H, R^e or R^f. The substituents Y^2, Q and Z in formula VIIIc are as defined in any of formulas (I) to (In) and any of the embodiments as described herein.

Organic Synthetic Techniques

[0130] A wide array of organic synthetic techniques exist in the art to facilitate the construction of potential modulators. Many of these organic synthetic methods are described in detail in standard reference sources utilized by those skilled in the art. One example of such a reference is March, 1994, Advanced Organic Chemistry; Reactions, Mechanisms and Structure, New York, McGraw Hill. Thus, the techniques useful to synthesize a potential modulator of kinase function are readily available to those skilled in the art of organic chemical synthesis.

Alternative Compound Forms or Derivatives

[0131] Compounds contemplated herein are described with reference to both generic formulae and specific compounds. In addition, invention compounds may exist in a number of different forms or derivatives, all within the scope of the present invention. Alternative forms or derivatives, include, for example, (a) prodrugs, and active metabolites (b) tautomers, isomers (including stereoisomers and regioisomers), and racemic mixtures (c) pharmaceutically acceptable salts and (d) solid forms, including different crystal forms, polymorphic or amorphous solids, including hydrates and solvates thereof, and other forms.

(a) *Prodrugs and Metabolites*

[0132] In addition to the present formulae and compounds described herein, the invention also includes prodrugs (generally pharmaceutically acceptable prodrugs), active metabolic derivatives (active metabolites), and their pharmaceutically acceptable salts.

[0133] Prodrugs are compounds or pharmaceutically acceptable salts thereof which, when metabolized under physiological conditions or when converted by solvolysis, yield the desired active compound. Prodrugs include, without limitation, esters, amides, carbamates, carbonates, ureides, solvates, or hydrates of the active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide one or more advantageous handling, administration, and/or metabolic properties. For example, some prodrugs are esters of the active compound; during metabolysis, the ester group is cleaved to yield the active drug. Esters include, for example, esters of a carboxylic acid group, or S-acyl or O-acyl derivatives of thiol, alcohol, or phenol groups. In this context, a common example is an alkyl ester of a carboxylic acid. Prodrugs may also include variants wherein an -NH group of the compound has undergone acylation, such as the 1-position of the 1H-pyrrolo[2,3-b]pyridine ring, or the nitrogen of the sulfonamide group of compounds as described herein, where cleavage of the acyl group provides the free -NH group of the active drug. Some prodrugs are activated enzymatically to yield the active compound, or a compound may undergo further chemical reaction to yield the active compound. Prodrugs may proceed from prodrug form to active form in a single step or may have one or more intermediate forms which may themselves have activity or may be inactive.

[0134] As described in *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, CA, 2001), prodrugs can be conceptually divided into two non-exclusive categories, bioprecursor prodrugs and carrier prodrugs. Generally, bioprecursor prodrugs are compounds that are inactive or have low activity compared to the corresponding active drug compound, that contain one or more protective groups and are converted to an active form by metabolism or solvolysis. Both the active drug form and any released metabolic products should have acceptably low toxicity. Typically,

the formation of active drug compound involves a metabolic process or reaction that is one of the following types:

[0135] Oxidative reactions: Oxidative reactions are exemplified without limitation by reactions such as oxidation of alcohol, carbonyl, and acid functionalities, hydroxylation of aliphatic carbons, hydroxylation of alicyclic carbon atoms, oxidation of aromatic carbon atoms, oxidation of carbon-carbon double bonds, oxidation of nitrogen-containing functional groups, oxidation of silicon, phosphorus, arsenic, and sulfur, oxidative N-dealkylation, oxidative O- and S-dealkylation, oxidative deamination, as well as other oxidative reactions.

[0136] Reductive reactions: Reductive reactions are exemplified without limitation by reactions such as reduction of carbonyl functionalitites, reduction of alcohol functionalities and carbon-carbon double bonds, reduction of nitrogen-containing functional groups, and other reduction reactions.

[0137] Reactions without change in the oxidation state: Reactions without change in the state of oxidation are exemplified without limitation by reactions such as hydrolysis of esters and ethers, hydrolytic cleavage of carbon-nitrogen single bonds, hydrolytic cleavage of non-aromatic heterocycles, hydration and dehydration at multiple bonds, new atomic linkages resulting from dehydration reactions, hydrolytic dehalogenation, removal of hydrogen halide molecule, and other such reactions.

[0138] Carrier prodrugs are drug compounds that contain a transport moiety, e.g., that improves uptake and/or localized delivery to a site(s) of action. Desirably for such a carrier prodrug, the linkage between the drug moiety and the transport moiety is a covalent bond, the prodrug is inactive or less active than the drug compound, the prodrug and any release transport moiety are acceptably non-toxic. For prodrugs where the transport moiety is intended to enhance uptake, typically the release of the transport moiety should be rapid. In other cases, it is desirable to utilize a moiety that provides slow release, e.g., certain polymers or other moieties, such as cyclodextrins. (See, e.g., Cheng et al., U.S. Patent Publ. No. 20040077595, App. No. 10/656,838, incorporated herein by reference.) Such carrier prodrugs are often advantageous for orally administered drugs. In some instances, the transport moiety provides targeted delivery of the drug, for example the drug may be conjugated to an antibody or antibody fragment. Carrier prodrugs can, for example, be used to improve one or more of the following properties: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity, decreased toxicity and adverse reactions, and/or improvement in drug formulation (e.g., stability, water solubility, suppression of an undesirable organoleptic or physiochemical property). For example, lipophilicity can be increased by esterification of hydroxyl groups with lipophilic carboxylic acids, or of carboxylic acid groups with alcohols, e.g., aliphatic alcohols. Wermuth, *supra*.

[0139] Metabolites, e.g., active metabolites, overlap with prodrugs as described above, e.g., bioprecursor prodrugs. Thus, such metabolites are pharmacologically active compounds or compounds that further metabolize to pharmacologically active compounds that are derivatives resulting from metabolic processes in the body of a subject. Of these, active metabolites are such pharmacologically active derivative compounds. For prodrugs, the prodrug compound is generally inactive or of lower activity than the metabolic product. For active metabolites, the parent compound may be either an active compound or may be an inactive prodrug. For example, in some compounds, one or more alkoxy groups can be metabolized to hydroxyl groups while retaining pharmacologic activity and/or carboxyl groups can be esterified, e.g., glucuronidation. In some cases, there can be more than one metabolite, where an intermediate metabolite(s) is further metabolized to provide an active metabolite. For example, in some cases a derivative compound resulting from metabolic glucuronidation may be inactive or of low activity, and can be further metabolized to provide an active metabolite.

[0140] Metabolites of a compound may be identified using routine techniques known in the art, and their activities determined using tests such as those described herein. See, e.g., Bertolini et al., 1997, *J. Med. Chem.*, 40:2011-2016; Shan et al., 1997, *J Pharm Sci* 86(7):756-757; Bagshawe, 1995, *Drug Dev. Res.*, 34:220-230; Wermuth, *supra*.

(b) *Tautomers, Stereoisomers, and Regioisomers*

[0141] It is understood that some compounds may exhibit tautomerism. In such cases, the formulae provided herein expressly depict only one of the possible tautomeric forms. It is therefore to be understood that the formulae provided herein are intended to represent any tautomeric form of the depicted compounds and are not to be limited merely to the specific tautomeric form depicted by the drawings of the formulae.

[0142] Likewise, some of the compounds according to the present invention may exist as stereoisomers, i.e. having the same atomic connectivity of covalently bonded atoms yet differing in the spatial orientation of the atoms. For example, compounds may be optical stereoisomers, which contain one or more chiral centers, and therefore, may exist in two or more stereoisomeric forms (e.g. enantiomers or diastereomers). Thus, such compounds may be present as single stereoisomers (i.e., essentially free of other stereoisomers), racemates, and/or mixtures of enantiomers and/or diastereomers. As another example, stereoisomers include geometric isomers, such as *cis*- or *trans*-orientation of substituents on adjacent carbons of a double bond. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention. Unless specified to the contrary, all such steroisomeric forms are included within the formulae provided herein.

[0143] In some embodiments, a chiral compound of the present invention is in a form that contains at least 80% of a single isomer (60% enantiomeric excess ("e.e.") or diastereomeric excess ("d.e.")), or at least 85% (70% e.e. or d.e.), 90% (80% e.e. or d.e.), 95% (90% e.e. or d.e.), 97.5% (95% e.e. or d.e.), or 99% (98% e.e. or d.e.). As generally understood by those skilled in the art, an optically pure compound having one chiral center is one that consists essentially of one of the two possible enantiomers (i.e., is enantiomerically pure), and an optically pure compound having more than one chiral center is one that is both diastereomerically pure and enantiomerically pure. In some embodiments, the compound is present in optically pure form, such optically pure form being prepared and/or isolated by methods known in the art (e.g. by recrystallization techniques, chiral synthetic techniques (including synthesis from optically pure starting materials), and chromatographic separation using a chiral column.

(c) *Pharmaceutically acceptable salts*

[0144] Unless specified to the contrary, specification of a compound herein includes pharmaceutically acceptable salts of such compound. Thus, compounds described herein and recited in any of the claims can be in the form of pharmaceutically acceptable salts, or can be formulated as pharmaceutically acceptable salts. Contemplated pharmaceutically acceptable salt forms include, without limitation, mono, bis, tris, tetrakis, and so on. Pharmaceutically acceptable salts are non-toxic in the amounts and concentrations at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of a compound without preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug. A compound of the invention may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly can react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

[0145] Pharmaceutically acceptable salts include acid addition salts such as those containing chloride, bromide, iodide, hydrochloride, acetate, phenylacetate, acrylate, ascorbate, aspartate, benzoate, 2-phenoxybenzoate, 2-acetoxybenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, bicarbonate, butyne-1,4 dioate, hexyne-1,6-dioate, caproate, caprylate, chlorobenzoate, cinnamate, citrate, decanoate, formate, fumarate, glycolate, gluconate, glucarate, glucuronate, glucose-6-phosphate, glutamate, heptanoate, hexanoate, isethionate, isobutyrate, gamma-hydroxybutyrate, phenylbutyrate, lactate, malate, maleate, hydroxymaleate, methylmaleate, malonate, mandelate, nicotinate, nitrate, isonicotinate, octanoate, oleate, oxalate, pamoate, phosphate, monohydrogenphosphate, dihydrogenphosphate, orthophosphate, metaphosphate, pyrophosphate, 2-phosphoglycerate, 3-phosphoglycerate, phthalate, propionate, phenylpropionate, propiolate, pyruvate, quinate, salicylate, 4-aminosalicylate, sebacate, stearate,

suberate, succinate, sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, sulfamate, sulfonate, benzenesulfonate (i.e. besylate), ethanesulfonate (i.e. esylate), ethane-1,2-disulfonate, 2-hydroxyethanesulfonate (i.e. isethionate), methanesulfonate (i.e. mesylate), naphthalene-1-sulfonate, naphthalene-2-sulfonate (i.e. napsylate), propanesulfonate, *p*-toluenesulfonate (i.e. tosylate), xylenesulfonates, cyclohexylsulfamate, tartrate, and trifluoroacetate. These pharmaceutically acceptable acid addition salts can be prepared using the appropriate corresponding acid.

[0146] When acidic functional groups, such as carboxylic acid or phenol are present, pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chloroprocaine, choline, ethanolamine, diethanolamine, triethanolamine, t-butylamine, dicyclohexylamine, ethylenediamine, N,N'-dibenzylethylenediamine, meglumine, hydroxyethylpyrrolidine, piperidine, morpholine, piperazine, procaine, aluminum, calcium, copper, iron, lithium, magnesium, manganese, potassium, sodium, zinc, ammonium, and mono-, di-, or tri-alkylamines (e.g. diethylamine), or salts derived from amino acids such as L-histidine, L-glycine, L-lysine, and L-arginine. For example, see *Remington's Pharmaceutical Sciences*, 19th ed., Mack Publishing Co., Easton, PA, Vol. 2, p. 1457, 1995. These pharmaceutically acceptable base addition salts can be prepared using the appropriate corresponding base.

[0147] Pharmaceutically acceptable salts can be prepared by standard techniques. For example, the free-base form of a compound can be dissolved in a suitable solvent, such as an aqueous or aqueous-alcohol solution containing the appropriate acid and then isolated by evaporating the solution. In another example, a salt can be prepared by reacting the free base and acid in an organic solvent. If the particular compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an appropriate inorganic or organic base.

(d) *Other compound forms*

[0148] In the case of agents that are solids, it is understood by those skilled in the art that the compounds and salts may exist in different crystal or polymorphic forms, or may be formulated as co-crystals, or may be in an amorphous form, or may be any combination thereof (e.g. partially crystalline, partially amorphous, or mixtures of polymorphs) all of which are intended to be within the scope of the present invention and specified formulae. Whereas salts are formed by acid/base addition, i.e. a free base or free acid of the compound of interest forms an acid/base reaction with a corresponding addition base or addition acid, respectively, resulting in an ionic charge interaction, co-crystals are a new chemical species that is formed between neutral compounds, resulting in the compound and an additional molecular species in the same crystal structure.

[0149] In some instances, compounds of the invention are complexed with an acid or a base, including base addition salts such as ammonium, diethylamine, ethanolamine, ethylenediamine,

diethanolamine, t-butylamine, piperazine, meglumine; acid addition salts, such as acetate, acetylsalicylate, besylate, camsylate, citrate, formate, fumarate, glutarate, hydrochlorate, maleate, mesylate, nitrate, oxalate, phosphate, succinate, sulfate, tartrate, thiocyanate and tosylate; and amino acids such as alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine or valine. In combining the compound of the invention with the acid or base, an amorphous complex is preferably formed rather than a crystalline material such as a typical salt or co-crystal. In some instances, the amorphous form of the complex is facilitated by additional processing, such as by spray-drying, mechanochemical methods such as roller compaction, or microwave irradiation of the parent compound mixed with the acid or base. Such methods may also include addition of ionic and/or non-ionic polymer systems, including, but not limited to, hydroxypropyl methyl cellulose acetate succinate (HPMCAS) and methacrylic acid copolymer (e.g. Eudragit® L100-55), that further stabilize the amorphous nature of the complex. Such amorphous complexes provide several advantages. For example, lowering of the melting temperature relative to the free base facilitiates additional processing, such as hot melt extrusion, to further improve the biopharmaceutical properties of the compound. Also, the amorphous complex is readily friable, which provides improved compression for loading of the solid into capsule or tablet form.

[0150] Additionally, the formulae are intended to cover hydrated or solvated as well as unhydrated or unsolvated forms of the identified structures. For example, the indicated compounds include both hydrated and non-hydrated forms. Other examples of solvates include the structures in combination with a suitable solvent, such as isopropanol, ethanol, methanol, dimethyl sulfoxide, ethyl acetate, acetic acid, or ethanolamine.

IV. Formulations and Administration

[0151] In another aspect, the present invention provides pharmaceutical compositions comprising/including a pharmaceutically acceptable carrier or excipient and a compound of the invention described herein or a pharmaceutically acceptable salt or solvate thereof. In an exemplary embodiment, the present invention provides a pharmaceutical formulation comprising/including a compound as described herein. In one embodiment, the compound has any of formulas I, and Ia to In.

[0152] The methods and compounds will typically be used in therapy for human subjects. However, they may also be used to treat similar or identical indications in other animal subjects. Compounds described herein can be administered by different routes, including injection (i.e. parenteral, including intravenous, intraperitoneal, subcutaneous, and intramuscular), oral, transdermal, transmucosal, rectal, or inhalant. Such dosage forms should allow the compound to reach target cells. Other factors are well known in the art, and include considerations such as toxicity and dosage forms that retard the compound or composition from exerting its effects. Techniques and formulations

generally may be found in Remington: *The Science and Practice of Pharmacy*, 21st edition, Lippincott, Williams and Wilkins, Philadelphia, PA, 2005 (hereby incorporated by reference herein).

[0153] In some embodiments, compositions will comprise pharmaceutically acceptable carriers or excipients, such as fillers, binders, disintegrants, glidants, lubricants, complexing agents, solubilizers, and surfactants, which may be chosen to facilitate administration of the compound by a particular route. Examples of carriers include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, types of starch, cellulose derivatives, gelatin, lipids, liposomes, nanoparticles, and the like. Carriers also include physiologically compatible liquids as solvents or for suspensions, including, for example, sterile solutions of water for injection (WFI), saline solution, dextrose solution, Hank's solution, Ringer's solution, vegetable oils, mineral oils, animal oils, polyethylene glycols, liquid paraffin, and the like. Excipients may also include, for example, colloidal silicon dioxide, silica gel, talc, magnesium silicate, calcium silicate, sodium aluminosilicate, magnesium trisilicate, powdered cellulose, macrocrystalline cellulose, carboxymethyl cellulose, cross-linked sodium carboxymethylcellulose, sodium benzoate, calcium carbonate, magnesium carbonate, stearic acid, aluminum stearate, calcium stearate, magnesium stearate, zinc stearate, sodium stearyl fumarate, syloid, stearowet C, magnesium oxide, starch, sodium starch glycolate, glyceryl monostearate, glyceryl dibehenate, glyceryl palmitostearate, hydrogenated vegetable oil, hydrogenated cotton seed oil, castor seed oil mineral oil, polyethylene glycol (e.g. PEG 4000-8000), polyoxyethylene glycol, poloxamers, povidone, crospovidone, croscarmellose sodium, alginic acid, casein, methacrylic acid divinylbenzene copolymer, sodium docusate, cyclodextrins (e.g. 2-hydroxypropyl-.delta.-cyclodextrin), polysorbates (e.g. polysorbate 80), cetrimide, TPGS (d-alpha-tocopheryl polyethylene glycol 1000 succinate), magnesium lauryl sulfate, sodium lauryl sulfate, polyethylene glycol ethers, di-fatty acid ester of polyethylene glycols, or a polyoxyalkylene sorbitan fatty acid ester (e.g., polyoxyethylene sorbitan ester Tween®), polyoxyethylene sorbitan fatty acid esters, sorbitan fatty acid ester, e.g. a sorbitan fatty acid ester from a fatty acid such as oleic, stearic or palmitic acid, mannitol, xylitol, sorbitol, maltose, lactose, lactose monohydrate or lactose spray dried, sucrose, fructose, calcium phosphate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, dextrates, dextran, dextrin, dextrose, cellulose acetate, maltodextrin, simethicone, polydextrosem, chitosan, gelatin, HPMC (hydroxypropyl methyl celluloses), HPC (hydroxypropyl cellulose), hydroxyethyl cellulose, and the like.

[0154] Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.5 mg to 1 g, preferably 1 mg to 700 mg, more preferably 5 mg to 100 mg of a compound of the invention (as a free-base, solvate (including hydrate) or salt, in any form), depending on the condition being treated, the route of administration, and the age, weight and condition of the patient. Preferred unit dosage formulations are those containing a daily dose, weekly dose, monthly dose, a sub-dose or

an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

[0155] Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including capsules, tablets, liquid-filled capsules, disintegrating tablets, immediate, delayed and controlled release tablets, oral strips, solutions, syrups, buccal and sublingual), rectal, nasal, inhalation, topical (including transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s), excipient(s) or diluent. Generally, the carrier, excipient or diluent employed in the pharmaceutical formulation is "non-toxic," meaning that it/they is/are deemed safe for consumption in the amount delivered in the pharmaceutical composition, and "inert" meaning that it/they does/do not appreciably react with or result in an undesired effect on the therapeutic activity of the active ingredient.

[0156] In some embodiments, oral administration may be used. Pharmaceutical preparations for oral use can be formulated into conventional oral dosage forms such as discret units capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops. Compounds described herein may be combined with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain, for example, tablets, coated tablets, hard capsules, soft capsules, solutions (e.g. aqueous, alcoholic, or oily solutions) and the like. Suitable excipients are, in particular, fillers such as sugars, including lactose, glucose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, corn starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone); oily excipients, including vegetable and animal oils, such as sunflower oil, olive oil, or codliver oil. The oral dosage formulations may also contain disintegrating agents, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid, or a salt thereof such as sodium alginate; a lubricant, such as talc or magnesium stearate; a plasticizer, such as glycerol or sorbitol; a sweetening such as sucrose, fructose, lactose, or aspartame; a natural or artificial flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring; or dye-stuffs or pigments, which may be used for identification or characterization of different doses or combinations, such as unit dosages. Also provided are dragee cores with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain, for example, gum arabic, talc, poly-vinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Oral fluids such as solutions, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound.

[0157] Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin ("gelcaps"), as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols.

[0158] In some embodiments, injection (parenteral administration) may be used, *e.g.*, intramuscular, intravenous, intraperitoneal, and/or subcutaneous. Compounds described herein for injection may be formulated in sterile liquid solutions, preferably in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. Dispersions may also be prepared in non-aqueous solutions, such as glycerol, propylene glycol, ethanol, liquid polyethylene glycols, triacetin, and vegetable oils. Solutions may also contain a preservative, such as methylparaben, propylparaben, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In addition, the compounds may be formulated in solid form, including, for example, lyophilized forms, and redissolved or suspended prior to use. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use.

[0159] In some embodiments, transmucosal, topical or transdermal administration may be used. In such formulations of compounds described herein, penetrants appropriate to the barrier to be permeated are used. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays or suppositories (rectal or vaginal). Compositions of compounds described herein for topical administration may be formulated as oils, creams, lotions, ointments, and the like by choice of appropriate carriers known in the art. Suitable carriers include vegetable or mineral oils, white petrolatum (white soft paraffin), branched chain fats or oils, animal fats and high molecular weight alcohol (greater than C_{12}). In some embodiments, carriers are selected such that the active ingredient is soluble. Emulsifiers, stabilizers, humectants and antioxidants may also be included as well as agents imparting color or fragrance, if desired. Creams for topical application are preferably formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture the active ingredient, dissolved in a small amount of solvent (e.g., an oil), is admixed. Additionally, administration by transdermal means may comprise a transdermal patch or dressing such as a bandage impregnated with an active ingredient and optionally one or more carriers or diluents known in the art. To be administered in the form of a transdermal delivery system, the dosage administration will be continuous rather than intermittent throughout the dosage regimen.

[0160] In some embodiments, compounds are administered as inhalants. Compounds described herein may be formulated as dry powder or a suitable solution, suspension, or aerosol. Powders and solutions may be formulated with suitable additives known in the art. For example, powders may include a suitable powder base such as lactose or starch, and solutions may comprise propylene glycol, sterile water, ethanol, sodium chloride and other additives, such as acid, alkali and buffer salts. Such solutions or suspensions may be administered by inhaling via spray, pump, atomizer, or nebulizer, and the like. The compounds described herein may also be used in combination with other inhaled therapies, for example corticosteroids such as fluticasone proprionate, beclomethasone dipropionate, triamcinolone acetonide, budesonide, and mometasone furoate; beta agonists such as albuterol, salmeterol, and formoterol; anticholinergic agents such as ipratroprium bromide or tiotropium; vasodilators such as treprostinal and iloprost; enzymes such as DNAase; therapeutic proteins; immunoglobulin antibodies; an oligonucleotide, such as single or double stranded DNA or RNA, siRNA; antibiotics such as tobramycin; muscarinic receptor antagonists; leukotriene antagonists; cytokine antagonists; protease inhibitors; cromolyn sodium; nedocril sodium; and sodium cromoglycate.

[0161] The amounts of various compounds to be administered can be determined by standard procedures taking into account factors such as the compound activity (*in vitro*, e.g. the compound IC_{50} vs. target, or *in vivo* activity in animal efficacy models), pharmacokinetic results in animal models (e.g. biological half-life or bioavailability), the age, size, and weight of the subject, and the disorder associated with the subject. The importance of these and other factors are well known to those of ordinary skill in the art. Generally, a dose will be in the range of about 0.01 to 50 mg/kg, also about 0.1 to 20 mg/kg of the subject being treated. Multiple doses may be used.

[0162] The compounds described herein may also be used in combination with other therapies for treating the same disease. Such combination use includes administration of the compounds and one or more other therapeutics at different times, or co-administration of the compound and one or more other therapies. In some embodiments, dosage may be modified for one or more of the compounds of the invention or other therapeutics used in combination, e.g., reduction in the amount dosed relative to a compound or therapy used alone, by methods well known to those of ordinary skill in the art.

[0163] It is understood that use in combination includes use with other therapies, drugs, medical procedures etc., where the other therapy or procedure may be administered at different times (e.g. within a short time, such as within hours (e.g. 1, 2, 3, 4-24 hours), or within a longer time (e.g. 1-2 days, 2-4 days, 4-7 days, 1-4 weeks)) than a compound described herein, or at the same time as a compound described herein. Use in combination also includes use with a therapy or medical procedure that is administered once or infrequently, such as surgery, along with a compound described herein administered within a short time or longer time before or after the other therapy or procedure. In some embodiments, the present invention provides for delivery of a compound

described herein and one or more other drug therapeutics delivered by a different route of administration or by the same route of administration. The use in combination for any route of administration includes delivery of a compound described herein and one or more other drug therapeutics delivered by the same route of administration together in any formulation, including formulations where the two compounds are chemically linked in such a way that they maintain their therapeutic activity when administered. In one aspect, the other drug therapy may be co-administered with a compound described herein. Use in combination by co-administration includes administration of co-formulations or formulations of chemically joined compounds, or administration of two or more compounds in separate formulations within a short time of each other (e.g. within an hour, 2 hours, 3 hours, up to 24 hours), administered by the same or different routes. Co-administration of separate formulations includes co-administration by delivery via one device, for example the same inhalant device, the same syringe, etc., or administration from separate devices within a short time of each other. Co-formulations of a compound described herein and one or more additional drug therapies delivered by the same route includes preparation of the materials together such that they can be administered by one device, including the separate compounds combined in one formulation, or compounds that are modified such that they are chemically joined, yet still maintain their biological activity. Such chemically joined compounds may have a linkage that is substantially maintained *in vivo*, or the linkage may break down *in vivo*, separating the two active components.

V. Kinase targets and indications of the invention

[0164] Protein kinases play key roles in propagating biochemical signals in diverse biological pathways. More than 500 kinases have been described, and specific kinases have been implicated in a wide range of diseases or conditions (i.e., indications), including for example without limitation, cancer, cardiovascular disease, inflammatory disease, neurological disease, and other diseases. As such, kinases represent important control points for small molecule therapeutic intervention. Specific target protein kinases contemplated by the present invention are described in the art, including, without limitation, protein kinases as described in US Patent Application Serial number 11/473,347 (see also, PCT publication WO2007002433), the disclosure of which is hereby incorporated by reference as it relates to such kinase targets, as well as the following:

[0165] **A-Raf:** Target kinase A-Raf (i.e., v-raf murine sarcoma 3611 viral oncogene homolog 1) is a 67.6 kDa serine/threonine kinase encoded by chromosome Xp11.4-p11.2 (symbol: ARAF). The mature protein comprises RBD (i.e., Ras binding domain) and phorbol-ester/DAG-type zinc finger domain and is involved in the transduction of mitogenic signals from the cell membrane to the nucleus. A-Raf inhibitors may be useful in treating neurologic diseases such as multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease (AD), Parkinson's disease; neoplastic diseases including, but not limited to, melanoma, glioma, sarcoma, carcinoma (e.g. colorectal, lung, breast, pancreatic, thyroid, renal, ovarian), lymphoma (e.g. histiocytic lymphoma), neurofibromatosis,

myelodysplastic syndrome, leukemia, tumor angiogenesis; pain of neuropathic or inflammatory origin, including acute pain, chronic pain, cancer-related pain and migraine; and diseases associated with muscle regeneration or degeneration, including, but not limited to, vascular restenosis, sarcopenia, muscular dystrophies (including, but not limited to, Duchenne, Becker, Emery-Dreifuss, Limb-Girdle, Facioscapulohumeral, Myotonic, Oculopharyngeal, Distal and Congenital Muscular Dystrophies), motor neuron diseases (including, but not limited to, amyotrophic lateral sclerosis, infantile progressive spinal muscular atrophy, intermediate spinal muscular atrophy, juvenile spinal muscular atrophy, spinal bulbar muscular atrophy, and adult spinal muscular atrophy), inflammatory myopathies (including, but not limited to, dermatomyositis, polymyositis, and inclusion body myositis), diseases of the neuromuscular junction (including, but not limited to, myasthenia gravis, Lambert-Eaton syndrome, and congenital myasthenic syndrome), myopathies due to endocrine abnormalities (including, but not limited to, hyperthyroid myopathy and hypothyroid myopathy) diseases of peripheral nerve (including, but not limited to, Charcot-Marie-Tooth disease, Dejerine-Sottas disease, and Friedreich's ataxia), other myopathies (including, but not limited to, myotonia congenita, paramyotonia congenita, central core disease, nemaline myopathy, myotubular myopathy, and periodic paralysis), and metabolic diseases of muscle (including, but not limited to, phosphorylase deficiency, acid maltase deficiency, phosphofructokinase deficiency, debrancher enzyme deficiency, mitochondrial myopathy, carnitine deficiency, carnitine palmatyl transferase deficiency, phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, lactate dehydrogenase deficiency, and myoadenylate deaminase deficiency).

[0166] **B-Raf:** Target kinase B-Raf (i.e., v-raf murine sarcoma viral oncogene homolog B1) is a 84.4 kDa serine/threonine kinase encoded by chromosome 7q34 (symbol: BRAF). The mature protein comprises RBD (i.e., Ras binding domain), C1 (i.e., protein kinase C conserved region 1) and STK (i.e., serine/threonine kinase) domains.

[0167] Target kinase B-Raf is involved in the transduction of mitogenic signals from the cell membrane to the nucleus and may play a role in the postsynaptic responses of hippocampal neurons. As such, genes of the RAF family encode kinases that are regulated by Ras and mediate cellular responses to growth signals. Indeed, B-Raf kinase is a key component of the RAS->Raf-> MEK->ERK/MAP kinase signaling pathway, which plays a fundamental role in the regulation of cell growth, division and proliferation, and, when constitutively activated, causes tumorigenesis. Among several isoforms of Raf kinase, the B-type, or B-Raf, is the strongest activator of the downstream MAP kinase signaling.

[0168] The BRAF gene is frequently mutated in a variety of human tumors, especially in malignant melanoma and colon carcinoma. The most common reported mutation was a missense thymine (T) to adenine (A) transversion at nucleotide 1796 (T1796A; amino acid change in the B-Raf protein is Val<600> to Glu<600>) observed in 80% of malignant melanoma tumors. Functional analysis

reveals that this transversion is the only detected mutation that causes constitutive activation of B-Raf kinase activity, independent of RAS activation, by converting B-Raf into a dominant transforming protein. Based on precedents, human tumors develop resistance to kinase inhibitors by mutating a specific amino acid in the catalytic domain as the "gatekeeper". (Balak, et. al., Clin Cancer Res. 2006, 12:6494-501). Mutation of Thr-529 in BRAF to Ile is thus anticipated as a mechanism of resistance to BRAF inhibitors, and this can be envisioned as a transition in codon 529 from ACC to ATC.

[0169] Niihori et al., report that in 43 individuals with cardio-facio-cutaneous (CFC) syndrome, they identified two heterozygous KRAS mutations in three individuals and eight BRAF mutations in 16 individuals, suggesting that dysregulation of the RAS-RAF-ERK pathway is a common molecular basis for the three related disorders (Niihori et al., Nat Genet. 2006, 38(3):294-6).

[0170] Many cancers associated with dysregulation of the RAS-RAF-ERK pathway, such as cancers having B-Raf V600, such as V600E mutations or NRAS mutations, may be treated with Raf kinase inhibitors, such as the Pan Raf kinase inhibitors as described herein. The ability of these compounds to inhibit multiple Raf kinase targets, including c-Raf-1, B-Raf, and B-Raf V600, such as V600E, provides additional benefits for inhibiting activating mutations in this pathway, with such cancers less likely to develop resistance to such inhibitors as they are targeting several points in the pathway. Pan Raf kinase inhibitors as described herein may be useful in treating a variety of cancers, including, but not limited to, melanoma, glioma, glioblastoma mulitforme, pilocytic astrocytoma, carcinoma (e.g. gastrointestinal, liver, biliary tract, bile duct (cholangiocarcinoma), colorectal, lung, brain, bladder, gallbladder, breast, pancreatic, thyroid, kidney, ovarian, adrenocortical, prostate), gastrointestinal stromal tumors, medullary thyroid cancer, tumor angiogenesis, acute myeloid leukemia, chronic myelomonocytic leukemia, childhood acute lymphoblastic leukemia, plasma cell leukemia, and multiple myeloma. See McDermott et al., PNAS, 2007, 104(50): 19936-19941; and Jaiswal et al., PLoS One, 2009, 4(5):e5717.

[0171] **c-Raf-1:** Target kinase c-Raf-1 (i.e., v-raf murine sarcoma viral oncogene homolog 1) is a 73.0 kDa STK encoded by chromosome 3p25 (symbol: RAF1). c-Raf-1 can be targeted to the mitochondria by BCL2 (i.e., oncogene B-cell leukemia 2) which is a regulator of apoptotic cell death. Active c-Raf-1 improves BCL2-mediated resistance to apoptosis, and c-Raf-1 phosphorylates BAD (i.e., BCL2-binding protein). c-Raf-1 is implicated in carcinomas, including colorectal, ovarian, lung and renal cell carcinoma. c-Raf-1 is also implicated as an important mediator of tumor angiogenesis (Hood, J.D. et al., 2002, Science **296**, 2404). c-Raf-1 inhibitors may also be useful for the treatment of acute myeloid leukemia and myelodysplastic syndromes (Crump, Curr Pharm Des 2002, 8(25):2243-8). c-Raf-1 activators may be useful as treatment for neuroendocrine tumors, such as medullary thyroid cancer, carcinoid, small cell lung cancer and pheochromocytoma (Kunnimalaiyaan et al., Anticancer Drugs 2006, 17(2):139-42).

[0172] Raf inhibitors (A-Raf and/or B-Raf and/or c-Raf-1) may be useful in treating A-Raf-mediated, B-Raf-mediated or c-Raf-1-mediated diseases or conditions selected from the group consisting of neurologic diseases, including, but not limited to, multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease (AD), Parkinson's disease, seizures and epilepsy; neoplastic diseases including, but not limited to, melanoma, glioma, glioblastoma multiforme, pilocytic astrocytoma, sarcoma, carcinoma (e.g. gastrointestinal, liver, biliary tract, bile duct (cholangiocarcinoma), colorectal, lung, brain, bladder, gallbladder, breast, pancreatic, thyroid, renal, ovarian, adrenocortical, prostate), lymphoma (e.g. histiocytic lymphoma) neurofibromatosis, acute myeloid leukemia, myelodysplastic syndrome, leukemia, chronic myelomonocytic leukemia, childhood, acute lymphoblastic leukemia, plasma cell leukemia, multiple myeloma, tumor angiogenesis, gastrointestinal stromal tumors, neuroendocrine tumors such as medullary thyroid cancer, carcinoid, small cell lung cancer, Kaposi's sarcoma, and pheochromocytoma; pain of neuropathic or inflammatory origin, including, but not limited to, acute pain, chronic pain, cancer-related pain, and migraine; cardiovascular diseases including, but not limited to, heart failure, ischemic stroke, cardiac hypertrophy, thrombosis (e.g. thrombotic microangiopathy syndromes), atherosclerosis, and reperfusion injury; inflammation and/or proliferation including, but not limited to, psoriasis, eczema, arthritis and autoimmune diseases and conditions, osteoarthritis, endometriosis, scarring, vascular restenosis, fibrotic disorders, rheumatoid arthritis, inflammatory bowel disease (IBD); immunodeficiency diseases, including, but not limited to, organ transplant rejection, graft versus host disease, and Kaposi's sarcoma associated with HIV; renal, cystic, or prostatic diseases, including, but not limited to, diabetic nephropathy, polycystic kidney disease, nephrosclerosis, glomerulonephritis, prostate hyperplasia, polycystic liver disease, tuberous sclerosis, Von Hippel Lindau disease, medullary cystic kidney disease, nephronophthisis, and cystic fibrosis; metabolic disorders, including, but not limited to, obesity; infection, including, but not limited to *Helicobacter pylori, Hepatitis* and *Influenza* viruses, fever, HIV, and sepsis; pulmonary diseases including, but not limited to, chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS); genetic developmental diseases, including, but not limited to, Noonan's syndrome, Costello syndrome, (faciocutaneoskeletal syndrome), LEOPARD syndrome, cardio-faciocutaneous syndrome (CFC), and neural crest syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair and endocrine diseases; and diseases associated with muscle regeneration or degeneration, including, but not limited to, sarcopenia, muscular dystrophies (including, but not limited to, Duchenne, Becker, Emery-Dreifuss, Limb-Girdle, Facioscapulohumeral, Myotonic, Oculopharyngeal, Distal and Congenital Muscular Dystrophies), motor neuron diseases (including, but not limited to, amyotrophic lateral sclerosis, infantile progressive spinal muscular atrophy, intermediate spinal muscular atrophy, juvenile spinal muscular atrophy, spinal bulbar muscular atrophy, and adult spinal muscular atrophy), inflammatory myopathies (including, but not limited to, dermatomyositis, polymyositis, and inclusion body myositis), diseases of the neuromuscular junction (including, but not limited to, myasthenia gravis, Lambert-Eaton syndrome, and congenital myasthenic syndrome), myopathies due to endocrine

abnormalities (including, but not limited to, hyperthyroid myopathy and hypothyroid myopathy) diseases of peripheral nerve (including, but not limited to, Charcot-Marie-Tooth disease, Dejerine-Sottas disease, and Friedreich's ataxia), other myopathies (including, but not limited to, myotonia congenita, paramyotonia congenita, central core disease, nemaline myopathy, myotubular myopathy, and periodic paralysis), and metabolic diseases of muscle (including, but not limited to, phosphorylase deficiency, acid maltase deficiency, phosphofructokinase deficiency, debrancher enzyme deficiency, mitochondrial myopathy, carnitine deficiency, carnitine palmatyl transferase deficiency, phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, lactate dehydrogenase deficiency, and myoadenylate deaminase deficiency).

[0173] **Erk2:** Target kinase Erk2 (i.e., extracellular signal-regulated kinase 2) is a 41.4 kDa dual function serine/threonine-tyrosine kinase encoded by chromosome 22q11.2 (symbol: MAPK1). Erk2 is a member of the mitogen-activated protein (MAP) kinase family and is alternatively known as mitogen-activated protein kinase 1 (i.e., MAPK1). MAP kinases act as an integration point for multiple biochemical signals, and are involved in a wide variety of cellular processes such as proliferation, differentiation, transcription regulation and development.

[0174] The activation of Erk2 requires phosphorylation by upstream kinases. Upon activation, Erk2 translocates to the nucleus of the stimulated cells, where it phosphorylates nuclear targets, in addition to other targets including microtubule associated protein 2, myelin basic protein and ELK1. MacKenzie et al. state that the cAMP-specific phosphodiesterase family 4, subfamily D, isoform 3 (i.e., PDE4D3) is shown to have FQF (i.e., Phe-Gln-Phe) and KIM (i.e., Kinase Interaction Motif) docking sites for Erk2. These sites straddle the Ser(579) target residue for Erk2 phosphorylation of PDE4D3. Mutation of either or both of these docking sites prevent Erk2 from being co-immunoprecipitated with PDE4D3, ablate the ability of epidermal growth factor (EGF) to inhibit PDE4D3 through Erk2 action in transfected COS cells, and attenuate the ability of Erk2 to phosphorylate PDE4D3 in vitro. The two conserved NH(2)-terminal blocks of sequence, called upstream conserved regions 1 and 2 (i.e., UCR1 and UCR2), that characterize PDE4 long isoforms, are proposed to amplify the small, inherent inhibitory effect that Erk2 phosphorylation exerts on the PDE4D catalytic unit. In contrast to this, the lone intact UCR2 region found in PDE4D1 directs COOH-terminal Erk2 phosphorylation to cause the activation of this short isoform. From the analysis of PDE4D3 truncates, it is suggested that UCR1 and UCR2 provide a regulatory signal integration module that serves to orchestrate the functional consequences of Erk2 phosphorylation. The PDE4D gene thus encodes a series of isoenzymes that are either inhibited or activated by Erk2 phosphorylation and thereby offers the potential for ERK2 activation either to increase or decrease cAMP levels in cellular compartments (MacKenzie et al., J Biol Chem 2000, 275(22):16609-17).

[0175] According to OMIM, Pleschka et al. (Nature Cell Biol., 2001, 3: 301-305) proposed that Erk2 regulates a cellular factor involved in the viral nuclear export protein function. They suggested

that local application of MEK inhibitors may have only minor toxic effects on the host while inhibiting viral replication without giving rise to drug-resistant virus variants (OMIM MIM Number: 176948: 10/27/2005). Erk2 is involved in cytokine signaling and is a target for treating inflammation. Ramesh and Philipp state that lipoproteins are the key inflammatory molecule type of Borrelia burgdorferi, the spirochete that causes Lyme disease. They investigated whether specific inhibition of p38 and Erk1/2 MAPK would inhibit TNF-alpha and IL-6 production and thus astrocyte apoptosis, and proliferation, respectively. Lipoprotein-stimulated IL-6 production was unaffected by the MAPK inhibitors. In contrast, inhibition of both p38 and Erk1/2 significantly diminished TNF-alpha production, and totally abrogated production of this cytokine when both MAPK pathways were inhibited simultaneously. MAPK inhibition thus may be considered as a strategy to control inflammation and apoptosis in Lyme neuroborreliosis (Ramesh and Philipp, Neurosci Lett 2005, 384(1-2):112-6). The role of Erk2 in signaling of cell differentiation, proliferation and survival suggests that inhibition of Erk2 may be therapeutic for several types of cancer. Husain et al. studied the effect of NSAIDs on MAPK activity and phosphorylation in gastric cancer. They conclude that NS-398 (a selective COX-2 inhibitor) and indomethacin (a non-selective NSAID) significantly inhibit proliferation and growth of human gastric cancer cell line MKN28. This effect is mediated by NSAID-induced inhibition of MAPK (ERK2) kinase signaling pathway, essential for cell proliferation (Husain et al., Life Sci 2001, 69(25-6):3045-54). Erk2 inhibitors may be useful in treating cancer, including gastric cancer, and in treating inflammation, including control of inflammation and apoptosis in Lyme neuroborreliosis.

Kinase Activity Assays

[0176] A number of different assays for kinase activity can be utilized for assaying for active modulators and/or determining specificity of a modulator for a particular kinase or group or kinases. In addition to the assay mentioned in the Examples below, one of ordinary skill in the art will know of other assays that can be utilized and can modify an assay for a particular application. For example, numerous papers concerning kinases describe assays that can be used.

[0177] In certain embodiments, compounds as disclosed herein are active in an assay measuring B-Raf protein kinase activity. In some embodiments, a compound as described herein has an IC_{50} of less than 1,000 nM, less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted B-Raf kinase activity assay. In some embodiments, a compound as described herein has an IC_{50} of less than 1,000 nM, less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted mutant B-Raf kinase (such as V600A, V600M, V600R, V600E, V600K or V600G) activity assay. In some embodiments the assay for measuring B-Raf kinase activity and/or mutant B-Raf kinase (such as V600A, V600M, V600R, V600E, V600K or

V600G) activity includes an assay (e.g., biochemical or cell-bases assays) such as described in Example 9 or an assay well known in the art similar to those described in Example 9.

[0178] In some embodiments, compounds as described herein have little or no activity in an assay measuring activation of the ERK pathway (i.e., in stimulating the phosphorylation of ERK 1/2). In some embodiments, compounds as described herein have an EC_{50} in an ERK activation assay that is greater than 1 μM; or greater than 2 μM; or greater than 3 μM; or greater than 4 μM; or greater than 5 μM; or greater than 8 μM; or greater than 10 μM. In certain embodiments, the assay for measuring activation of the ERK pathway includes an assay (e.g., biochemical or cell-bases assays) such as described in Example 9 or one or more assays well known in the art for measuring ERK activity similar to that described in Example 9.

[0179] In some embodiments, compounds as described herein are active in an assay measuring B-Raf protein kinase activity and/or an assay for measuring mutant B-Raf (such as V600A, V600M, V600R, V600E, V600K or V600G) protein kinase activity, and have little or no activity in an assay measuring activation of the ERK pathway. In some embodiments a compound as described herein has an IC_{50} of less than 1,000 nM, less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted B-Raf kinase activity assay (including a mutant B-Raf kinase activity assay) and an EC_{50} in an ERK activation assay that is greater than 1 μM; or greater than 2 μM; or greater than 3 μM; or greater than 4 μM; or greater than 5 μM; or greater than 8 μM; or greater than 10 μM. In some embodiments, a compound as described herein has an IC_{50} of less than 100 nM in a V600A, V600M, V600R, V600E, V600K or V600G mutant B-Raf activity assay and an EC_{50} of greater than 10 in an ERK activation assay.

VI. Methods for Treating Conditions Mediated by Kinases

[0180] In another aspect, the present invention provides a method for treating a subject suffering from or at risk of a protein kinase mediated diseases or conditions. The method includes administering to the subject an effective amount of a compound of any of formulas I and Ia to In, or a compound as described herein, or a composition comprising any of formulas I and Ia to In and any of the compounds described herein or a pharmaceutically acceptable salt or a solvate or hydrate thereof. In certain embodiments, the method involves administering to the subject an effective amount of any one or more compound(s) as described herein in combination with one or more other therapies for the disease or condition.

[0181] In some embodiments, the diseases or conditions treatable with the compounds of the present invention include, but are not limited to, multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease (AD), Parkinson's disease, seizures and epilepsy; neoplastic diseases including, but not limited to, melanoma, glioma, glioblastoma multiforme, pilocytic astrocytoma, sarcoma,

carcinoma (e.g. gastrointestinal, liver, biliary tract, bile duct (cholangiocarcinoma), colorectal, lung, gallbladder, breast, pancreatic, thyroid, renal, ovarian, adrenocortical, prostate), lymphoma (e.g. histiocytic lymphoma) neurofibromatosis, gastrointestinal stromal tumors, acute myeloid leukemia, myelodysplastic syndrome, leukemia, tumor angiogenesis, neuroendocrine tumors such as medullary thyroid cancer, carcinoid, small cell lung cancer, Kaposi's sarcoma, and pheochromocytoma; pain of neuropathic or inflammatory origin, including, but not limited to, acute pain, chronic pain, cancer-related pain, and migraine; cardiovascular diseases including, but not limited to, heart failure, ischemic stroke, cardiac hypertrophy, thrombosis (e.g. thrombotic microangiopathy syndromes), atherosclerosis, and reperfusion injury; inflammation and/or proliferation including, but not limited to, psoriasis, eczema, arthritis and autoimmune diseases and conditions, osteoarthritis, endometriosis, scarring, vascular restenosis, fibrotic disorders, rheumatoid arthritis, inflammatory bowel disease (IBD); immunodeficiency diseases, including, but not limited to, organ transplant rejection, graft versus host disease, and Kaposi's sarcoma associated with HIV; renal, cystic, or prostatic diseases, including, but not limited to, diabetic nephropathy, polycystic kidney disease, nephrosclerosis, glomerulonephritis, prostate hyperplasia, polycystic liver disease, tuberous sclerosis, Von Hippel Lindau disease, medullary cystic kidney disease, nephronophthisis, and cystic fibrosis; metabolic disorders, including, but not limited to, obesity; infection, including, but not limited to *Helicobacter pylori, Hepatitis* and *Influenza* viruses, fever, HIV, and sepsis; pulmonary diseases including, but not limited to, chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS); genetic developmental diseases, including, but not limited to, Noonan's syndrome, Costello syndrome, (faciocutaneoskeletal syndrome), LEOPARD syndrome, cardio-faciocutaneous syndrome (CFC), and neural crest syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair and endocrine diseases; and diseases associated with muscle regeneration or degeneration, including, but not limited to, sarcopenia, muscular dystrophies (including, but not limited to, Duchenne, Becker, Emery-Dreifuss, Limb-Girdle, Facioscapulohumeral, Myotonic, Oculopharyngeal, Distal and Congenital Muscular Dystrophies), motor neuron diseases (including, but not limited to, amyotrophic lateral sclerosis, infantile progressive spinal muscular atrophy, intermediate spinal muscular atrophy, juvenile spinal muscular atrophy, spinal bulbar muscular atrophy, and adult spinal muscular atrophy), inflammatory myopathies (including, but not limited to, dermatomyositis, polymyositis, and inclusion body myositis), diseases of the neuromuscular junction (including, but not limited to, myasthenia gravis, Lambert-Eaton syndrome, and congenital myasthenic syndrome), myopathies due to endocrine abnormalities (including, but not limited to, hyperthyroid myopathy and hypothyroid myopathy) diseases of peripheral nerve (including, but not limited to, Charcot-Marie-Tooth disease, Dejerine-Sottas disease, and Friedreich's ataxia), other myopathies (including, but not limited to, myotonia congenita, paramyotonia congenita, central core disease, nemaline myopathy, myotubular myopathy, and periodic paralysis), and metabolic diseases of muscle (including, but not limited to, phosphorylase deficiency, acid maltase deficiency, phosphofructokinase deficiency, debrancher enzyme deficiency, mitochondrial myopathy, carnitine deficiency, carnitine palmatyl transferase deficiency,

phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, lactate dehydrogenase deficiency, and myoadenylate deaminase deficiency). In one embodiment, the disease or condition is selected from the group consisting of melanoma, glioma, glioblastoma multiforme, pilocytic astrocytoma, sarcoma, liver cancer, biliary tract cancer, cholangiocarcinoma, colorectal cancer, lung cancer, gallbladder cancer, breast cancer, pancreatic cancer, thyroid cancer, renal cancer, ovarian cancer, adrenocortical cancer, prostate cancer, histiocytic lymphoma, neurofibromatosis, gastrointestinal stromal tumors, acute myeloid leukemia, myelodysplastic syndrome, leukemia, tumor angiogenesis, medullary thyroid cancer, carcinoid, small cell lung cancer, Kaposi's sarcoma, pheochromocytoma, acute pain, chronic pain, and polycystic kidney disease. In a preferred embodiment, the disease or condition is selected from the group consisting of melanoma, glioma, glioblastoma multiforme, pilocytic astrocytoma, colorectal cancer, thyroid cancer, lung cancer, ovarian cancer, prostate cancer, liver cancer, gallbladder cancer, gastrointestinal stromal tumors, biliary tract cancer, cholangiocarcinoma, acute pain, chronic pain, and polycystic kidney disease.

[0182] In other embodiments, the diseases or condictions treatable with the compounds of the present invention include, but are not limited to, ischemic stroke, cerebrovascular ischemia, multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, dementia, senile chorea, Huntington's disease, neoplastic disease, complications with neoplastic disease, chemotherapy-induced hypoxia, gastrointestinal stromal tumors, prostate tumors, mast cell tumors, canine mast cell tumors, acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, melanoma, mastocytosis, glioma, glioblastoma, astrocytoma, neuroblastoma, sarcomas, sarcomas of neuroectodermal origin, leiomyosarcoma, lung carcinoma, breast carcinoma, pancreatic carcinoma, colon carcinoma, hepatocellular carcinoma, renal carcinoma, carcinoma of the female genital tract, squamous cell carcinoma, carcinoma in situ, lymphoma, histiocytic lymphoma, non-Hodgkin's lymphoma, MEN2 syndromes, neurofibromatosis, Schwann cell neoplasia, myelodysplastic syndrome, leukemia, tumor angiogenesis, thyroid cancer, liver cancer, bone cancer, skin cancer, brain cancer, cancer of the central nervous system, pancreatic cancer, lung cancer, small cell lung cancer, non small cell lung cancer, breast cancer, colon cancer, bladder cancer, prostate cancer, gastrointestinal tract cancer, cancer of the endometrium, fallopian tubecancer, testicular cancer, ovarian cancer, pain of neuropathic origin, pain of inflammatory origin, acute pain, chronic pain, migraine, cardiovascular disease, heart failure, cardiac hypertrophy, thrombosis, thrombotic microangiopathy syndromes, atherosclerosis, reperfusion injury, ischemia, cerebrovascular ischemia, liver ischemia, inflammation, polycystic kidney disease, age-related macular degeneration, rheumatoid arthritis, allergic rhinitis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, Wegener's granulomatosis, psoriasis, scleroderma, chronic thyroiditis, Grave's disease, myasthenia gravis, multiple sclerosis, osteoarthritis, endometriosis, dermal scarring, tissue scarring, vascular restenosis, fibrotic disorders,

hypereosinophilia, CNS inflammation, pancreatitis, nephritis, atopic dermatitis, hepatitis, immunodeficiency diseases, severe combined immunodeficiency, organ transplant rejection, graft versus host disease, renal disease, prostatic disease, diabetic nephropathy, nephrosclerosis, glomerulonephritis, interstitial nephritis, Lupus nephritis, prostate hyperplasia, chronic renal failure, tubular necrosis, diabetes-associated renal complication, associated renal hypertrophy, type 1 diabetes, type 2 diabetes, metabolic syndrome, obesity, hepatic steatosis, insulin resistance, hyperglycemia, lipolysis obesity, infection, *Helicobacter pylori* infection, *Influenza virus* infection, fever, sepsis, pulmonary diseases, chronic obstructive pulmonary disease, acute respiratory distress syndrome, asthma, allergy, bronchitis, emphysema, pulmonary fibrosis, genetic developmental diseases, Noonan's syndrome, Crouzon syndrome, acrocephalo-syndactyly type I, Pfeiffer's syndrome, Jackson-Weiss syndrome, Costello syndrome, faciocutaneoskeletal syndrome, leopard syndrome, cardio-faciocutaneous syndrome, neural crest syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair or endocrine diseases, disorders of bone structure or mineralization, osteoporosis, increased risk of fracture, hypercalcemia, bone metastases, Grave's disease, Hirschsprung's disease, lymphoedema, selective T-cell defect, X-linked agammaglobulinemia, diabetic retinopathy, alopecia, erectile dysfunction, and tuberous sclerosis

[0183] In some embodiments, the disease is a cancer selected from the group consisting of melanoma, glioma, glioblastoma, pilocytic astrocytoma, liver cancer, biliary tract cancer, cholangiocarcinoma, colorectal cancer, lung cancer, bladder cancer, gallbladder cancer, breast cancer, pancreatic cancer, thyroid cancer, kidney cancer, ovarian cancer, adrenocortical cancer, prostate cancer, gastrointestinal stromal tumors, medullary thyroid cancer, tumor angiogenesis, acute myeloid leukemia, chronic myelomonocytic leukemia, childhood acute lymphoblastic leukemia, plasma cell leukemia, and multiple myeloma. In certain instances, the disease is a B-Raf V600, such as V600A, V600E, V600G, V600K , V600M or V600R mutant-mediated disease. In one embodiment, the disease is a V600E mutant mediated disease. In one embodiment, the disease is a cancer, preferably selected from the group consisting of melanoma, glioma, glioblastoma multiforme, pilocytic astrocytoma, colorectal cancer, thyroid cancer, lung cancer, ovarian cancer, prostate cancer, liver cancer, gallbladder cancer, gastrointestinal stromal tumors, biliary tract cancer, and cholangiocarcinoma. In one embodiment, the cancer is melanoma, colorectal cancer, thyroid cancer or lung cancer.

[0184] In some embodiments, the invention provides methods for treating any B-Raf protein kinase mediated disease or condition, including any B-Raf mutant kinase mediated disease or condition in an animal subject in need thereof, wherein the method involves administering to the subject an effective amount of any one or more compound(s) as described herein. In certain embodiments, the method involves administering to the subject an effective amount of any one or more compound(s) as described herein in combination with one or more other therapies for the disease or condition.

[0185] In some embodiments, the invention provides methods for treating any B-Raf V600 mutant protein kinase, such as V600A, V600E, V600G, V600K , V600M or V600R mutant protein kinase mediated disease or condition in an animal subject in need thereof, wherein the method involves administering to the subject an effective amount of any one or more compound(s) as described herein. In certain embodiments, the method involves administering to the subject an effective amount of any one or more compound(s) as described herein in combination with one or more other therapies for the disease or condition.

[0186] In some embodiments, a compound as described herein is a Raf kinase inhibitor and has an IC_{50} of less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted Raf kinase activity assay. In some embodiments, a compound as described herein will have an IC_{50} of less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM with respect to B-Raf, c-Raf-1, or B-Raf V600E mutant. In some embodiments, a compound as described herein will selectively inhibit one or more Raf kinases relative to one or more other Raf kinases.

[0187] In some embodiments, the invention provides a method for inhibiting a B-Raf V600 mutant protein kinase, such as V600A, V600E, V600G, V600K , V600M or V600R mutant protein kinase. The method includes contacting a compound of any of formulas I and Ia to In, or a compound as described herein, or a composition comprising any of formulas I and Ia to In and any of the compounds described herein or a pharmaceutically acceptable salt or a solvate thereof with a cell or a B-Raf V600 mutant protein kinase either in vitro or in vivo.

[0188] In certain embodiments, the invention provides use of a compound of any of formulas I and Ia to In, or a compound as described herein, or a composition comprising any of formulas I and Ia to In and any of the compounds described herein or a pharmaceutically acceptable salt or a solvate thereof in the manufacture of a medicament for the treatment of a disease or condition as described herein. In other embodiments, the invention provides a compound of any of formulas I and Ia to In, or a compound as described herein, or a composition comprising any of formulas I and Ia to In and any of the compounds described herein or a pharmaceutically acceptable salt or a solvate thereof for use in treating a disease or condition as described herein.

[0189] In some embodiments, the invention provides a method for suppressing UV induced cell apoptosis. The method includes contacting a cell with a compound of any of formulas I and Ia to In, or a compound as described herein, or a composition comprising any of formulas I and Ia to In and any of the compounds described herein or a pharmaceutically acceptable salt or a solvate thereof prior to subject the cell to UV exposure or radiation.

Combination Therapy

[0190] Protein kinase modulators may be usefully combined with another pharmacologically active compound, or with two or more other pharmacologically active compounds, particularly in the treatment of cancer. In one embodiment, the composition includes any one or more compound(s) as described herein along with one or more compounds that are therapeutically effective for the same disease indication, wherein the compounds have a synergistic effect on the disease indication. In one embodiment, the composition includes any one or more compound(s) as described herein effective in treating a cancer and one or more other compounds that are effective in treating the same cancer, further wherein the compounds are synergistically effective in treating the cancer.

[0191] In some embodiments, the invention provides a composition comprising a compound of any of formula (I) and formula Ia to formula In, or a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, and one or more agents. In some embodiments, the one or more agents are selected from an alkylating agent, including, but not limited to, adozelesin, altretamine, bendamustine, bizelesin, busulfan, carboplatin, carboquone, carmofur, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, estramustine, etoglucid, fotemustine, hepsulfam, ifosfamide, improsulfan, irofulven, lomustine, mannosulfan, mechlorethamine, melphalan, mitobronitol, nedaplatin, nimustine, oxaliplatin, piposulfan, prednimustine, procarbazine, ranimustine, satraplatin, semustine, streptozocin, temozolomide, thiotepa, treosulfan, triaziquone, triethylenemelamine, triplatin tetranitrate, trofosphamide, and uramustine; an antibiotic, including, but not limited to, aclarubicin, amrubicin, bleomycin, dactinomycin, daunorubicin, doxorubicin, elsamitrucin, epirubicin, idarubicin, menogaril, mitomycin, neocarzinostatin, pentostatin, pirarubicin, plicamycin, valrubicin, and zorubicin; an antimetabolite, including, but not limited to, aminopterin, azacitidine, azathioprine, capecitabine, cladribine, clofarabine, cytarabine, decitabine, floxuridine, fludarabine, 5-fluorouracil, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, nelarabine, pemetrexed, azathioprine, raltitrexed, tegafur-uracil, thioguanine, trimethoprim, trimetrexate, and vidarabine; an immunotherapy, including, but not limited to, alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, panitumumab, pertuzumab, rituximab, tositumomab, trastuzumab, 90 Y ibritumomab tiuxetan, ipilimumab, and tremelimumab; a hormone or hormone antagonist, including, but not limited to, anastrozole, androgens, buserelin, diethylstilbestrol, exemestane, flutamide, fulvestrant, goserelin, idoxifene, letrozole, leuprolide, magestrol, raloxifene, tamoxifen, and toremifene; a taxane, including, but not limited to, DJ-927, docetaxel, TPI 287, larotaxel, ortataxel, paclitaxel, DHA-paclitaxel, and tesetaxel; a retinoid, including, but not limited to, alitretinoin, bexarotene, fenretinide, isotretinoin, and tretinoin; an alkaloid, including, but not limited to, demecolcine, homoharringtonine, vinblastine, vincristine, vindesine, vinflunine, and vinorelbine; an antiangiogenic agent, including, but not limited to, AE-941 (GW786034, Neovastat), ABT-510, 2-methoxyestradiol, lenalidomide, and thalidomide; a topoisomerase inhibitor, including, but not limited to, amsacrine, belotecan, edotecarin, etoposide, etoposide phosphate, exatecan, irinotecan (also active metabolite SN-38 (7-ethyl-10-hydroxy-camptothecin)), lucanthone, mitoxantrone, pixantrone,

rubitecan, teniposide, topotecan, and 9-aminocamptothecin; a kinase inhibitor, including, but not limited to, axitinib (AG 013736), dasatinib (BMS 354825), erlotinib, gefitinib, flavopiridol, imatinib mesylate, lapatinib, motesanib diphosphate (AMG 706), nilotinib (AMN107), seliciclib, sorafenib, sunitinib malate, AEE-788, BMS-599626, UCN-01 (7-hydroxystaurosporine), and vatalanib; a targeted signal transduction inhibitor including, but not limited to bortezomib, geldanamycin, and rapamycin; a biological response modifier, including, but not limited to, imiquimod, interferon-α, and interleukin-2; and other chemotherapeutics, including, but not limited to 3-AP (3-amino-2-carboxyaldehyde thiosemicarbazone), altrasentan, aminoglutethimide, anagrelide, asparaginase, bryostatin-1, cilengitide, elesclomol, eribulin mesylate (E7389), ixabepilone, lonidamine, masoprocol, mitoguanazone, oblimersen, sulindac, testolactone, tiazofurin, mTOR inhibitors (e.g. temsirolimus, everolimus, deforolimus), PI3K inhibitors (e.g. BEZ235, GDC-0941, XL147, XL765), Cdk4 inhibitors (e.g. PD-332991), Akt inhibitors, Hsp90 inhibitors (e.g. tanespimycin) and farnesyltransferase inhibitors (e.g. tipifarnib); MEK inhibitors (e.g., AS703026, AZD6244 (selumetinib), AZD8330, BIX02188, CI1040 (PD184352), D-87503, GSK1120212 (JTP-74057), PD0325901, PD318088, PD98059, PDEA119 (BAY 869766), TAK-733). Preferably, the method of treating a cancer involves administering to the subject an effective amount of a composition including any one or more compound(s) as described herein in combination with a chemotherapeutic agent selected from capecitabine, 5-fluorouracil, carboplatin, dacarbazine, gefitinib, oxaliplatin, paclitaxel, SN-38, temozolomide, vinblastine, bevacizumab, cetuximab, interferon-α, interleukin-2, or erlotinib. In some embodiments, a protein kinase modulator, particularly a compound of any of formula (I) to formula In, or a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, as defined above, may be administered simultaneously, sequentially or separately in combination with one or more agents as described above.

[0192] In one embodiment, the invention provides methods for treating a disease or condition mediated by B-Raf kinase, including mutations thereof, by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein in combination with one or more other suitable therapies for treating the disease.

[0193] In one embodiment, the invention provides methods for treating a disease or condition mediated by B-Raf V600 mutant kinases, such as V600A, V600E, V600G, V600K , V600M or V600R mutant kinase, by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein in combination with one or more other suitable therapies for treating the disease. In one embodiment, the invention provides methods for treating a cancer mediated by B-Raf mutant kinases, such as V600A, V600E, V600G, V600M or V600R mutant by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein. In one embodiment, the invention provides methods for treating a cancer mediated by B-Raf mutant kinases, such as V600A, V600E, V600G, V600K , V600M or V600R mutant by administering to the subject an effective amount of a composition including any

one or more compound(s) as described herein in combination with one or more suitable anticancer therapies, such as one or more chemotherapeutic drugs. In one instance, the B-Raf mutant kinase is V600A. In another instance, the B-Raf mutant kinase is V600E. In yet another instance, the B-Raf mutant kinase is V600G. In another instance, the B-Raf mutant kinase is V600K. In another instance, the B-Raf mutant kinase is V600M. In another instance, the B-Raf mutant kinase is V600R.

[0194] In one embodiment, the invention provides a method of treating a cancer in a subject in need thereof by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein in combination with one or more other therapies or medical procedures effective in treating the cancer. Other therapies or medical procedures include suitable anticancer therapy (e.g. drug therapy, vaccine therapy, gene therapy, photodynamic therapy) or medical procedure (e.g. surgery, radiation treatment, hyperthermia heating, bone marrow or stem cell transplant). In one embodiment, the one or more suitable anticancer therapies or medical procedures is selected from treatment with a chemotherapeutic agent (e.g. chemotherapeutic drug), radiation treatment (e.g. x-ray, γ-ray, or electron, proton, neutron, or α particle beam), hyperthermia heating (e.g. microwave, ultrasound, radiofrequency ablation), Vaccine therapy (e.g. AFP gene hepatocellular carcinoma vaccine, AFP adenoviral vector vaccine, AG-858, allogeneic GM-CSF-secretion breast cancer vaccine, dendritic cell peptide vaccines), gene therapy (e.g. Ad5CMV-p53 vector, adenovector encoding MDA7, adenovirus 5-tumor necrosis factor alpha), photodynamic therapy (e.g. aminolevulinic acid, motexafin lutetium), surgery, or bone marrow and stem cell transplantation.

Kit

[0195] In another aspect, he invention provides kits that include a compound of any of formulas (I) to (In) or a compound as described herein or composition thereof as described herein. In some embodiments, the compound or composition is packaged, e.g., in a vial, bottle, flask, which may be further packaged, e.g., within a box, envelope, or bag; the compound or composition is approved by the U.S. Food and Drug Administration or similar regulatory agency for administration to a mammal, e.g., a human; the compound or composition is approved for administration to a mammal, e.g., a human, for a protein kinase mediated disease or condition; the invention kit may include written instructions for use and/or other indication that the compound or composition is suitable or approved for administration to a mammal, e.g., a human, for a Raf protein kinase-mediated disease or condition; and the compound or composition may be packaged in unit dose or single dose form, e.g., single dose pills, capsules, or the like.

VII. Examples

[0196] The following examples are offered to illustrate, but not to limit the claimed invention.

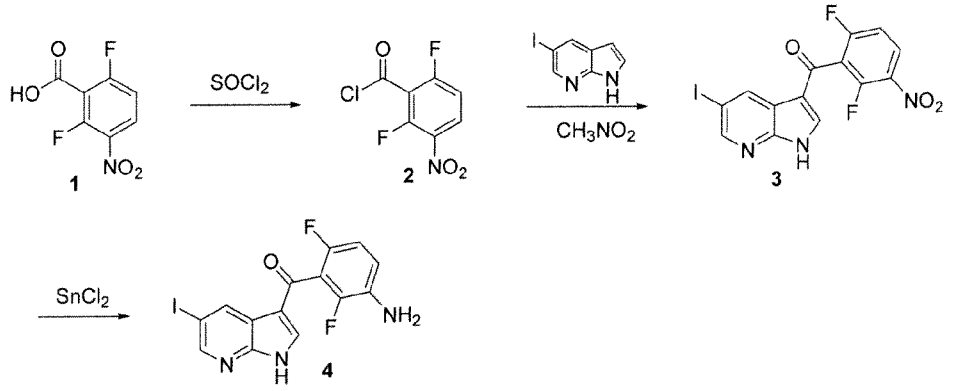
[0197] Compounds within the scope of this invention can be synthesized as described below, using a variety of reactions known to the skilled artisan. One skilled in the art will also recognize that alternative methods may be employed to synthesize the target compounds of this invention, and that the approaches described within the body of this document are not exhaustive, but do provide broadly applicable and practical routes to compounds of interest. In some examples, the mass spectrometry result indicated for a compound may have more than one value due to the isotope distribution of an atom in the molecule, such as a compound having a bromo or chloro substituent.

[0198] Certain molecules claimed in this patent can exist in different enantiomeric and diastereomeric forms and all such variants of these compounds are claimed.

[0199] Those skilled in the art will also recognize that during standard work up procedures in organic chemistry, acids and bases are frequently used. Salts of the parent compounds are sometimes produced, if they possess the necessary intrinsic acidity or basicity, during the experimental procedures described within this patent.

Example 1: Preparation of (3-Amino-2,6-difluorophenyl)(5-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (4)

Scheme 1



[0200] **Synthesis of 2,6-Difluoro-3-nitrobenzoyl chloride (2):** To 2,6-difluoro-3-nitrobenzoic acid (50 g, 246 mmol) was added thionyl chloride (185 mL, 2536 mmol). The reaction was heated at 80 °C overnight and allowed to cool to room temperature. The volatiles were removed under reduced pressure and then azeotroped from toluene several times to give an oil which was used directly in the next step.

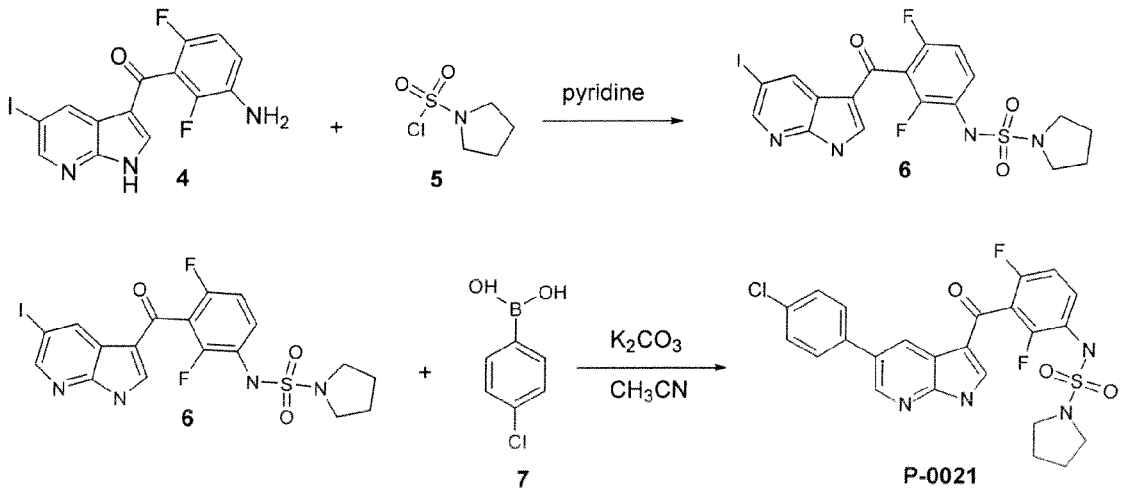
[0201] **Synthesis of (2,6-Difluoro-3-nitrophenyl)(5-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (3):** 5-Iodo-1H-pyrrolo[2,3-b]pyridine (32.8 g, 134 mmol) and aluminum chloride (108 g, 806 mmol) in nitromethane (340 mL) were allowed to stir at room temperature for 1 hour. Then 2,6-difluoro-3-nitrobenzoyl chloride (44.7 g, 202 mmol) in nitromethane (340 mL) was added and the mixture was heated at 50 °C for 5 days. After cooling to 0 °C, the reaction was quenched with

methanol (250 mL) resulting in a ppt. The mixture was diluted with water (500 mL) and then filtered. The crude product which was triturated with ethyl acetate and filtered washing with additional ethyl acetate to give (2,6-difluoro-3-nitrophenyl)(5-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (42 g, 98 mmol, 72.8 % yield) as a brown solid. ^{1}H NMR spectrum is consistent with the structure of the compound.

[0202] Synthesis of (3-Amino-2,6-difluorophenyl)(5-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (4): To (2,6-difluoro-3-nitrophenyl)(5-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (44.6 g, 104 mmol) in ethyl acetate (1732 mL) and THF (1732 mL) was treated portionwise with tin(II) chloride dihydrate (82 g, 364 mmol) while heating 60 °C and held at this temperature overnight. After cooling to room temperature, the reaction mixture was quenched with half sat. aqueous sodium bicarbonate and filtered through Celite washing the cake with ethyl acetate. The layers were separated and the organic layer was washed with brine then concentrated under reduced pressure to give the crude product which was triturated with DCM and filtered to give (3-amino-2,6-difluorophenyl)(5-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (34 g, 85 mmol, 82 % yield) as a tan solid. ^{1}H NMR spectrum is consistent with the structure of the compound.

Example 2: N-[3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide (P-0021).

Scheme 2



[0203] Synthesis of N-[2,4-difluoro-3-(5-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide (6): To (3-amino-2,6-difluoro-phenyl)-(5-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (**4**, 2.9 g, 7.27 mmol) in pyridine (11.2 mL), was added pyrrolidine-1-sulfonyl chloride (**5**, 1.68 mL, 14.53 mmol). The mixture was stirred at room temperature for 48 hours. The resulting mixture was poured into a saturated NH_4 Cl aqueous solution and extracted with ethyl acetate. The organic layers were combined and washed with brine, dried

over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography using an 80 g-cartridge (eluted with ethyl acetate and DCM). The desired product was obtained as a solid (**6**, 2.06 g, 53.3% yield). MS(ESI) $[M+H^+]^+$ = 532.8. ^1H NMR spectrum is consistent with the structure of the compound.

[0204] Synthesis of N-[3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide (P-0021): In a microwave vessel, N-[2,4-difluoro-3-(5-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide (**6**, 0.27g, 0.51 mmol) and (4-chlorophenyl)boronic acid (**7**, 0.1 g, 0.61 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (27 mg) were mixed in 1 M of potassium carbonate in water and acetonitrile (1.31 mL). The mixture was heated at 130 ° C under microwave for 15 minutes. The resulting mixture separated into an organic layer and aqueous layer. The aqueous layer was extracted with ethyl acetate and combined with the organic layer, washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by chromatography using a 40 g-cartridge (eluted with ethyl acetate and dichloromethane). The purified product was obtained as a solid (P-0021, 0.071 g, 27% yield). MS (ESI) $[M+H^+]^+$ = 517.0 and 519.0. ^1H NMR spectrum is consistent with the structure of the compound.

[0205] The following compounds were prepared according to the protocols set forth in Examples 1, 2 and 4-9 and Schemes 1, 2 and 4-9.

Table 2

5-chloro-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine, **(P-0012)**,

5-(4-chlorophenyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0013)**,

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0014)**,

N-[2,4-difluoro-3-(5-fluoro-4-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide **(P-0015)**,

5-chloro-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0018)**,

5-(4-chlorophenyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0019)**,

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0020)**,

N-[3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0021)**,

N-[3-[5-[2-(dimethylamino)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0022)**,

N-[2-fluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide **(P-0023)**

N-[2,4-difluoro-3-(5-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide **(P-0024)**,

3-[3-[[cyclopropyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0025)**,

[2-fluoro-3-(methylsulfamoylamino)phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone **(P-0026)**,

5-(4-cyanophenyl)-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(0027)**,

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine **(P-0028)**,

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-(6-methyl-3-pyridyl)-1H-pyrrolo[2,3-b]pyridine **(P-0029)**,

5-[6-(dimethylamino)-3-pyridyl]-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0030)**,

5-(4-cyanophenyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0031)**,

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine **(0032)**,

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(6-methyl-3-pyridyl)-1H-pyrrolo[2,3-b]pyridine **(0033)**,

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine **(0034)**,

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine **(P-0035)**,

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-phenyl-1H-pyrrolo[2,3-b]pyridine **(P-0036)**,

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-phenyl-1H-pyrrolo[2,3-b]pyridine **(P-0037)**,

5-bromo-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0038)**,

3-[2-fluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0040)**

3-benzyloxy-N-[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0041)**

1-cyclopropyl-N-[2-fluoro-3-[5-(1-methylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]methanesulfonamide (**P-0042**)

N-[2-fluoro-3-[5-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide (**P-0043**)

N-[3-[5-(2,4-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide (**P-0044**)

N-[2-fluoro-3-[5-(6-methyl-3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide (**P-0045**)

N-[3-[5-[6-(dimethylamino)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide (**P-0046**)

N-[2-fluoro-3-[5-(2-isopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide (**P-0047**)

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide (**P-0048**)

N-[3-[5-(4-cyano-3-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide (**P-0049**)

N-[3-[5-[4-(1-cyanocyclopropyl)phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide (**P-0050**)

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-(2-isopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0051**)

5-(2-cyclopropylpyrimidin-5-yl)-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0052**)

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-[6-(trifluoromethyl)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine (**P-0053**)

5-(4-cyano-3-methoxy-phenyl)-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0054**)

5-[4-(1-cyanocyclopropyl)phenyl]-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0055**)

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0056**)

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-isopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0057**)

5-(2-cyclopropylpyrimidin-5-yl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0058**)

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-[6-(trifluoromethyl)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine (**P-0059**)

5-(4-cyano-3-methoxy-phenyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0060**)

5-[4-(1-cyanocyclopropyl)phenyl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0061**)

N-[2-fluoro-3-[5-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide (**P-0062**)

N-[2-fluoro-3-(5-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide (**P-0063**)

5-[2-(cyclopropylamino)pyrimidin-5-yl]-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0064**)

N-[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]-2-methoxy-ethanesulfonamide (**P-0065**)

methyl 3-[[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]sulfamoyl]propanoate (**P-0066**)

N-[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]cyclopropanesulfonamide (**P-0067**)

[3-(ethylsulfamoylamino)-2-fluoro-phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (**P-0068**)

[3-(ethylsulfamoylamino)-2-fluoro-phenyl]-(5-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (**P-0069**)

3-[2-fluoro-3-[[isobutyl(methyl)sulfamoyl]amino]benzoyl]-5-iodo-1H-pyrrolo[2,3-b]pyridine (**P-0070**)

[2-fluoro-3-(isopropylsulfamoylamino)phenyl]-(5-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (**P-0071**)

3-[2-fluoro-3-[[isobutyl(methyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0072**)

3-[2-fluoro-3-[[2-methoxyethyl(methyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0073**)

N-[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]-2-methyl-pyrrolidine-1-sulfonamide (**P-0074**)

3-[2-fluoro-3-[[isopropyl(methyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0075**)

5-[6-(dimethylamino)-3-pyridyl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0076**)

5-[2-(cyclopropylamino)pyrimidin-5-yl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0077**)

5-(2-cyclopropylpyrimidin-5-yl)-3-[2,6-difluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0078**)

5-[4-(1-cyanocyclopropyl)phenyl]-3-[2,6-difluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0079**)

5-[4-(1-cyanocyclopropyl)phenyl]-3-[2-fluoro-3-[[2-methoxyethyl(methyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0080**)

5-[2-(cyclopropylamino)pyrimidin-5-yl]-3-[2-fluoro-3-[[2-methoxyethyl(methyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0081**)

5-[2-(cyclopropylamino)pyrimidin-5-yl]-3-[2-fluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0082**)

3-[3-[[cyclopropylmethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0083**)

3-[3-[[cyclopropylmethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0084**)

5-(2-cyclopropylpyrimidin-5-yl)-3-[2-fluoro-3-[[2-methoxyethyl(methyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0085**)

5-(2-cyclopropylpyrimidin-5-yl)-3-[2-fluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0086**)

5-(6-cyclopropyl-3-pyridyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0087**)

3,3-difluoro-N-[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]azetidine-1-sulfonamide (**P-0088**)

4-[[(1S)-1-cyclopropylethyl]amino]-5-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-7H-pyrrolo[2,3-d]pyrimidine (**P-0089**)

N-[3-[5-(4-cyanophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide (**P-0090**)

N-[3-[5-(2-cyanopyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide (**P-0091**)

N-[2-fluoro-3-[5-(2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide (**P-0092**)

N-[3-[5-(5-cyano-3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide (**P-0093**)

N-[3-[5-(6-cyano-3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide (**P-0094**)

N-[2-fluoro-3-[5-[6-(trifluoromethyl)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide (**P-0095**)

5-(2-cyanopyrimidin-5-yl)-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0096**)

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-(2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0097**)

5-(5-cyano-3-pyridyl)-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0098**)

5-(6-cyano-3-pyridyl)-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0099**)

5-(2-cyanopyrimidin-5-yl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0100**)

5-(5-cyano-3-pyridyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0101**)

5-(6-cyano-3-pyridyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0102**)

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-[4-(1-hydroxy-1-methyl-ethyl)phenyl]-1H-pyrrolo[2,3-b]pyridine (**P-0103**)

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-[4-(1-hydroxy-1-methyl-ethyl)phenyl]-1H-pyrrolo[2,3-b]pyridine (**P-0104**)

N-[2-fluoro-3-[5-[4-(1-hydroxy-1-methyl-ethyl)phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide (**P-0105**)

5-[2-(dimethylamino)pyrimidin-5-yl]-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0106**)

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0107**)

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0108**)

N-[2-fluoro-3-[5-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide (**P-0109**)

3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-iodo-1H-pyrrolo[2,3-b]pyridine (**P-0110**)

3-[2-fluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-5-(2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0111**)

3-[3-[[cyclopropylmethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0112**)

5-(6-cyclopropyl-3-pyridyl)-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0113**)

5-(6-cyclopropyl-3-pyridyl)-3-[2-fluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (**P-0114**)

3-[3-[[cyclopropylmethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(6-cyclopropyl-3-pyridyl)-1H-pyrrolo[2,3-b]pyridine (**P-0115**)

3-[2,6-difluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (**P-0116**)

[2-fluoro-3-(propylsulfamoylamino)phenyl]-(5-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (**P-0117**)

[2-fluoro-3-(propylsulfamoylamino)phenyl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone **(P-0223)**

N-[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]butane-2-sulfonamide **(P-0224)**

N-[2-fluoro-3-[5-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]butane-2-sulfonamide **(P-0225)**

N-[3-[5-[2-(cyclopropylamino)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]butane-2-sulfonamide **(P-0226)**

N-[3-[5-[4-(1-cyanocyclopropyl)phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]butane-2-sulfonamide **(P-00227)**

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]butane-2-sulfonamide **(P-0228)**

N-[2-fluoro-3-[5-(2-isopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]butane-2-sulfonamide **(P-0229)**

N-[3-[5-[6-(dimethylamino)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]butane-2-sulfonamide **(P-0230)**

N-[2-fluoro-3-[5-(2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]butane-2-sulfonamide **(P-0231)**

N-[3-[5-[2-(cyclopropylamino)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0232)**

5-(2-cyclopropylpyrimidin-5-yl)-3-[2-fluoro-3-[[isopropyl(methyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0233)**

N-[2-fluoro-3-[5-(2-morpholinopyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0235)**

N-[2-fluoro-3-[5-(2-morpholinopyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]butane-2-sulfonamide **(P-0236)**

5-[4-(1-cyanocyclopropyl)phenyl]-3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0237)**

5-(2-cyclopropylpyrimidin-5-yl)-3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0238)**

5-[4-(1-cyanocyclopropyl)phenyl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0239)**

5-(2-cyclopropylpyrimidin-5-yl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0240)**

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0241)**

[2-fluoro-3-(propylsulfamoylamino)phenyl]-[5-(1-methylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone **(P-0242)**

1-[4-[3-[2-fluoro-3-(pyrrolidin-1-ylsulfonylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]cyclopropanecarboxylic acid **(P-0243)**

3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-5-(5-ethoxypyrazin-2-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0244)**

5-[4-(1-cyano-1-methyl-ethyl)phenyl]-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0245)**

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]-3,3-dimethyl-pyrrolidine-1-sulfonamide **(P-0246)**

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]-3-methyl-pyrrolidine-1-sulfonamide **(P-0247)**;

N-[3-[5-[4-(1-cyanocyclopropyl)phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0248)**

3-[3-[[cyclopropyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0249)**

[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-[2-fluoro-3-(propylsulfamoylamino)phenyl]methanone **(P-0251)**

3-[3-[[cyclopropyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0252)**

1-[4-[3-[2-fluoro-3-(pyrrolidin-1-ylsulfonylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]cyclopropanecarboxamide **(P-0253)**

methyl 1-[4-[3-[2-fluoro-3-(pyrrolidin-1-ylsulfonylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]cyclopropanecarboxylate **(P-0254)**

5-[4-(1-cyano-1-methyl-ethyl)phenyl]-3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0255)**

5-(2-ethoxypyrimidin-5-yl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0256)**

ethyl 1-[[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]sulfamoyl]pyrrolidine-2-carboxylate **(P-0257)**

4-[5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyrimidin-2-yl]morpholine **(P-0258)**

4-[3-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]morpholine **(P-0259)**

N-[2,4-difluoro-3-[5-[2-(4-methylpiperazin-1-yl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0260)**

N-[2,4-difluoro-3-[5-(2-piperazin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0261)**

N-[2,4-difluoro-3-[5-[2-(4-hydroxy-1-piperidyl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0262)**

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-[2-(4-methylpiperazin-1-yl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine **(P-0263)**

tert-butyl 4-[5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyrimidin-2-yl]piperazine-1-carboxylate **(P-0264)**

N-[2,4-difluoro-3-[5-[2-(1-hydroxy-1-methyl-ethyl)thiazol-4-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0265)**

N-[2,4-difluoro-3-[5-(2-morpholinopyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0266)**

N-[1-[[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]sulfamoyl]pyrrolidin-3-yl]-N-methyl-acetamide **(P-0267)**

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(2-piperazin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0268)**

N-[3-[5-[2-(azetidin-1-yl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0269)**

N-[2,4-difluoro-3-[5-(2-methoxythiazol-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0270)**

(3R)-N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]-3-methyl-pyrrolidine-1-sulfonamide **(P-0271)**

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]-3-(methylamino)pyrrolidine-1-sulfonamide **(P-0272)**

N-[2,4-difluoro-3-[5-(4-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0273)**

N-[3-(5-cyclopropyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0274)**

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-[2-(4-hydroxy-1-piperidyl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridine **(P-0275)**

5-[3-(1-cyanocyclopropyl)phenyl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0276)**

5-[2-(azetidin-1-yl)pyrimidin-5-yl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0277)**

N-[3-[5-(2-aminopyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0279)**

N-[3-[5-(2-aminopyrimidin-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0280)**

N-[2-fluoro-3-[5-(4-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0281)**

N-[2,4-difluoro-3-[5-(2-morpholinopyrimidin-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0282)**

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(2-fluoro-4-pyridyl)-1H-pyrrolo[2,3-b]pyridine **(P-0283)**

N-[2,4-difluoro-3-[5-(2-morpholino-4-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0284)**

N-[2,4-difluoro-3-[5-[2-(4-methylpiperazin-1-yl)-4-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0285)**

N-[3-[5-[2-(cyclobutoxy)-4-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0286)**

N-[2,4-difluoro-3-[5-(2-methoxy-4-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0287)**

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]-3,3-difluoro-pyrrolidine-1-sulfonamide **(P-0288)**

(3S)-N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]-3-fluoro-pyrrolidine-1-sulfonamide **(P-0289)**

methyl 2-[[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]sulfamoyl]propanoate **(P-0291)**

5-[2-(dimethylamino)pyrimidin-5-yl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0292)**

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0293)**

N-[2,4-difluoro-3-[5-[6-(trifluoromethyl)pyrimidin-4-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0294)**

N-[3-[5-(2-cyclopropyl-4-pyridyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0295)**

5-cyclobutyl-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0297)**

5-cyclopropyl-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0298)**

N-[3-[5-(6-aminopyrimidin-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0299)**

5-(4-cyanophenyl)-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0300)**

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-[4-(trifluoromethyl)phenyl]-1H-pyrrolo[2,3-b]pyridine **(P-0301)**

5-[3-(dimethylamino)phenyl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0302)**

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(4-pyrrolidin-1-ylphenyl)-1H-pyrrolo[2,3-b]pyridine **(P-0303)**

2-[4-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]-5-methyl-1,3,4-oxadiazole **(P-0304)**

2-[4-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]-5-(methylamino)-1,3,4-thiadiazole **(P-0305)**

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-[5-(1-hydroxy-1-methyl-ethyl)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine **(P-0306)**

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-[6-(1-hydroxy-1-methyl-ethyl)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine **(P-0307)**

5-[4-(diethylamino)phenyl]-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0308)**

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(2-oxoindolin-6-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0309)**

3-[5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-thienyl]-5-methyl-1,2,4-oxadiazole **(P-0310)**

2-amino-6-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]quinazoline **(P-0311)**

N-cyclopropyl-5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide **(P-0312)**

2-(dimethylamino)-6-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]quinazoline **(P-0313)**

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-[4-(1-hydroxycyclopropyl)phenyl]-1H-pyrrolo[2,3-b]pyridine **(P-0314)**

5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]thiazole **(P-0315)**

4-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-(1-hydroxy-1-methyl-ethyl)thiazole **(P-0316)**

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(6-methoxypyridazin-3-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0317)**

N-[2,4-difluoro-3-[5-(6-morpholinopyrimidin-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0318)**

N-[2,4-difluoro-3-[5-[6-(4-methylpiperazin-1-yl)pyrimidin-4-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0319)**

(3S)-N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]-3-methyl-pyrrolidine-1-sulfonamide **(P-0320)**

N-[2-fluoro-3-[5-(6-morpholinopyrimidin-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0321)**

N-[2-fluoro-3-[5-[6-(4-methylpiperazin-1-yl)pyrimidin-4-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0322)**

N-[2-fluoro-3-[5-[6-(4-methylpiperazin-1-yl)-2-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0324)**

N-[2-fluoro-3-[5-(4-methoxypyrimidin-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0325)**

N-[2-fluoro-3-[5-(4-methylpyrimidin-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0326)**

(3R)-N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]-3-fluoro-pyrrolidine-1-sulfonamide **(P-0327)**

[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-[2,6-difluoro-3-(methylsulfamoylamino)phenyl]methanone **(P-0334)**

[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-[3-(ethylsulfamoylamino)-2,6-difluoro-phenyl]methanone **(P-0335)**

5-(2-cyclopropylpyrimidin-5-yl)-3-[2,6-difluoro-3-(sulfamoylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0336)**

N-[3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]butane-2-sulfonamide **(P-0337)**

(3R)-N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]-3-fluoro-pyrrolidine-1-sulfonamide **(P-0338)**

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]-3-fluoro-pyrrolidine-1-sulfonamide **(P-0339)**

5-(2-cyclopropylpyrimidin-5-yl)-3-[2,6-difluoro-3-[[methyl(2,2,2-trifluoroethyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0340)**

N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]butane-2-sulfonamide **(P-0342)**

5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-methoxy-thiazole **(P-0343)**

3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridine **(P-0344)**

N-[2,4-difluoro-3-[5-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]pyrrolidine-1-sulfonamide **(P-0345)**

N-[3-(5-cyclobutyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]pyrrolidine-1-sulfonamide **(P-0346)**

N-[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]cyclopropanesulfonamide **(P-0347)**

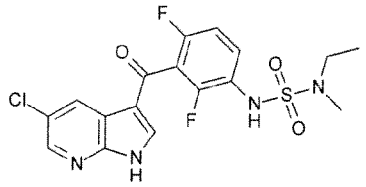
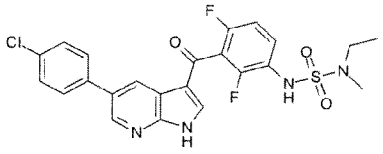
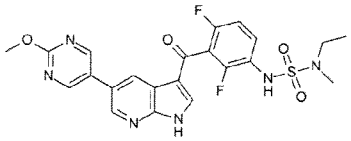
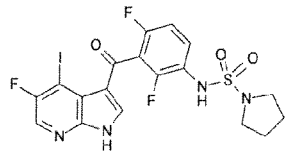
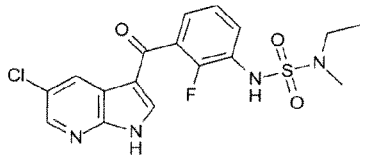
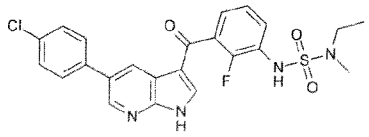
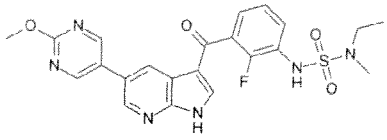
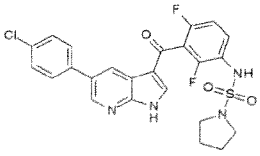
1-allyl-N-[3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]cyclopropanesulfonamide **(P-0348)**

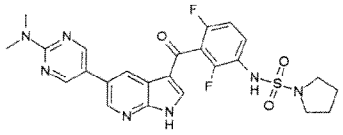
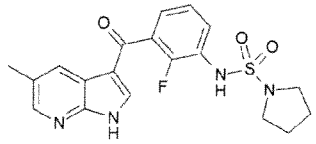
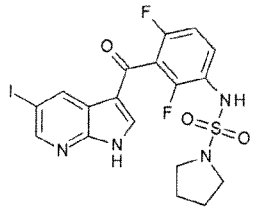
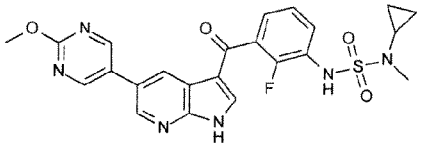
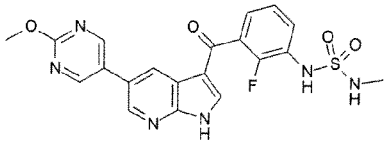
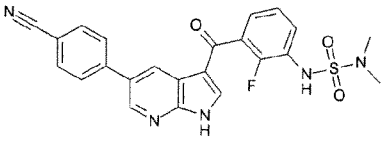
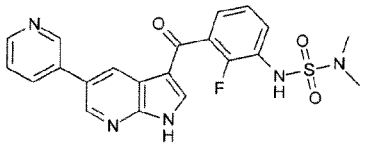
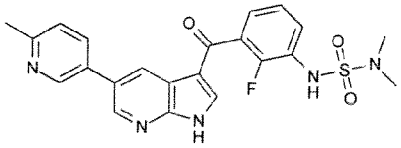
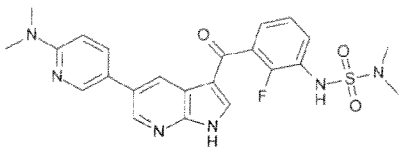
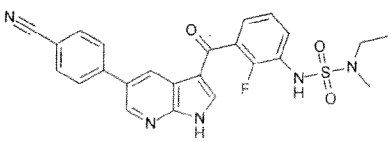
N-[2,4-difluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]cyclopropanesulfonamide **(P-0349)**

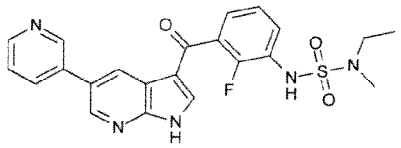
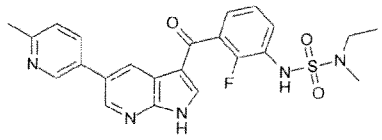
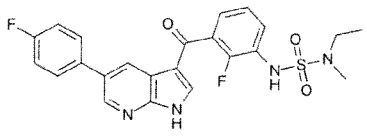
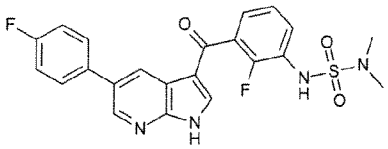
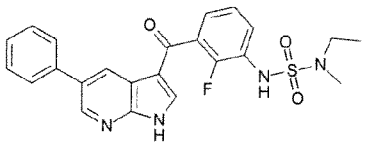
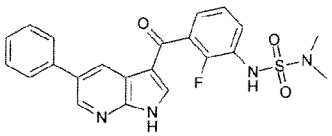
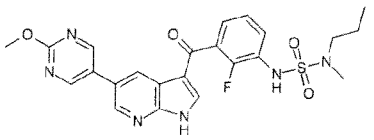
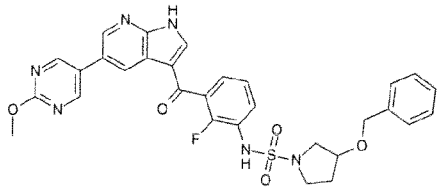
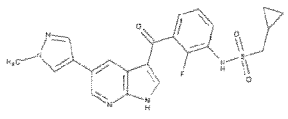
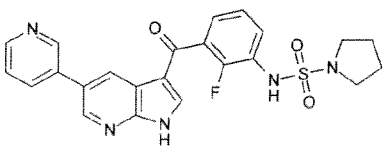
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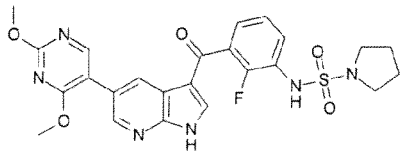
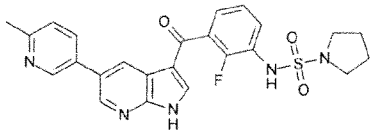
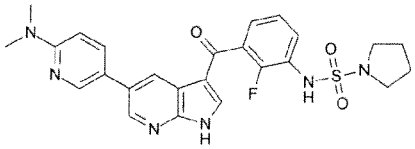
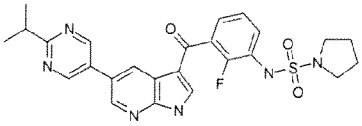
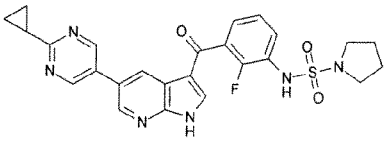
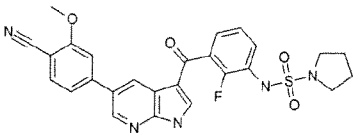
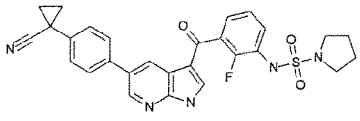
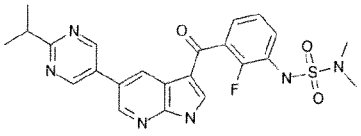
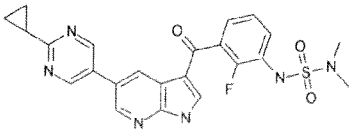
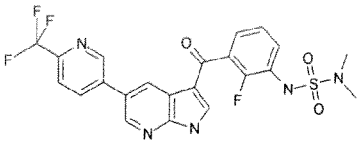
N-[3-(5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]cyclopropanesulfonamide **(P-0351)**

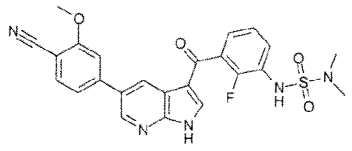
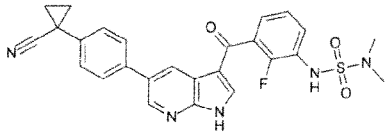
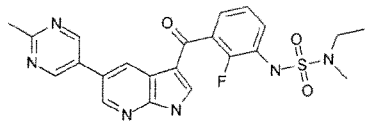
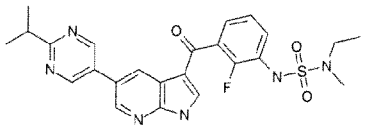
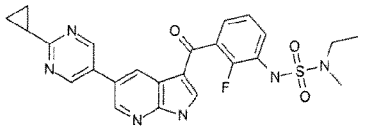
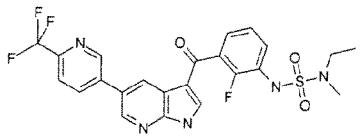
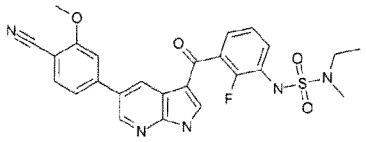
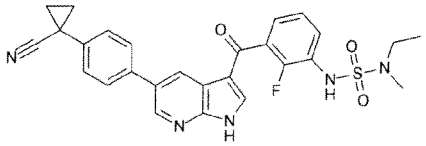
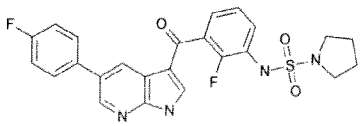
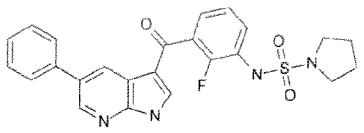
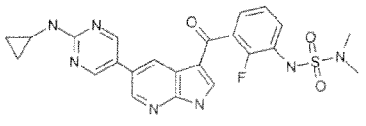
The following table provides structures of certain compounds of the present invention and observed mass. ^{1}H NMR spectra were consistent with the structures of the compounds.

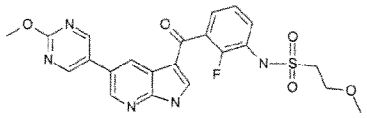
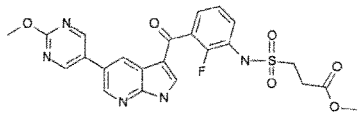
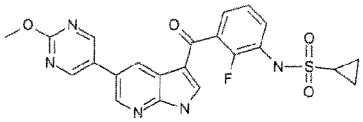
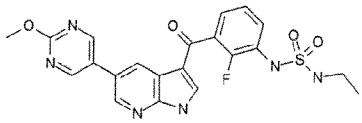
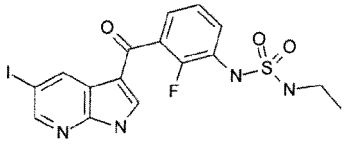
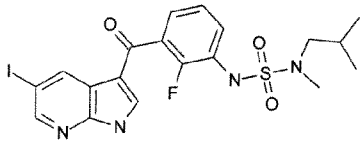
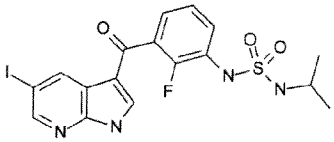
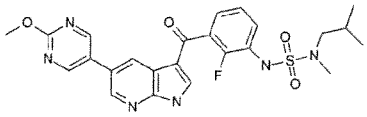
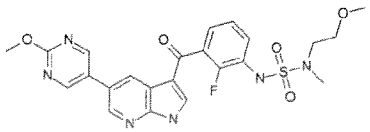
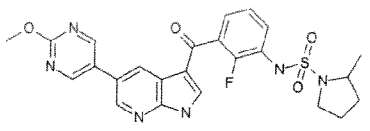
No.	Compounds	MS(ESI) $[M+H^+]^+$ observed
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P-0013		504.9
P-0014		503.0
P-0015		551.1
P-0018		410.9
P-0019		489.0
P-0020		485.1
P-0021		517.0 and 519.0

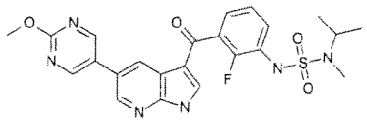
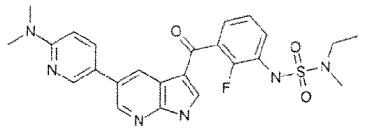
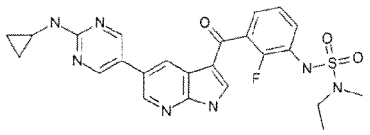
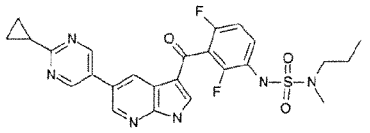
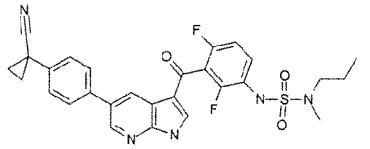
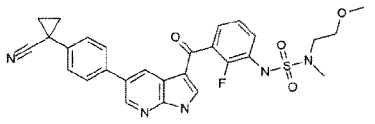
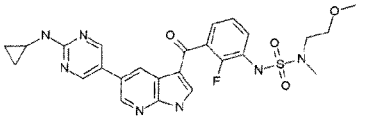
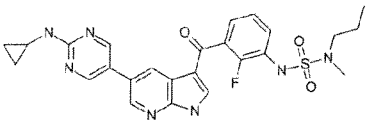
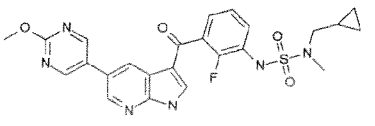
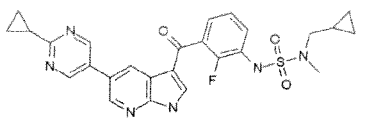
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P-0023		402.9
P-0024		532.8
P-0025		497.0
P-0026		457.0
P-0027		463.5
P-0028		439.5
P-0029		454.5
P-0030		483.5
P-0031		478.5

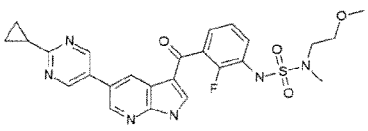
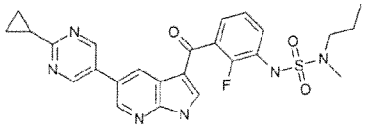
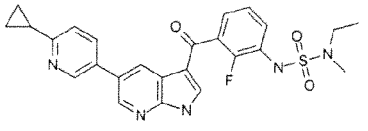
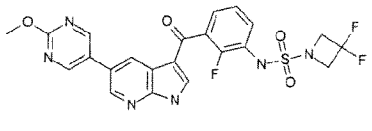
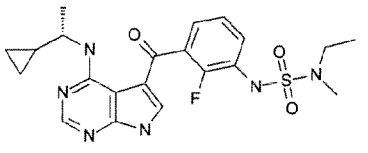
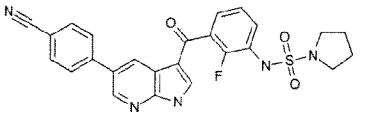
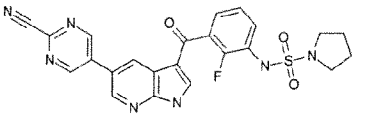
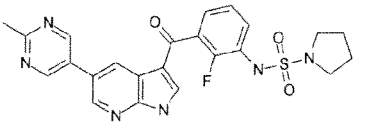
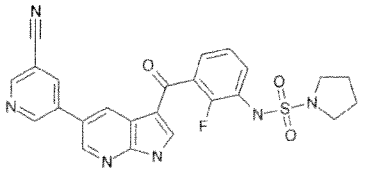
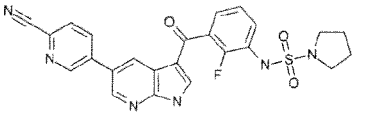
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P-0033		468.2
P-0034		471.5
P-0035		457.5
P-0036		453.1
P-0037		439.2
P-0040		499.0
P-0041		603.6
P-0042		454.0
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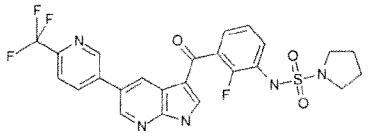
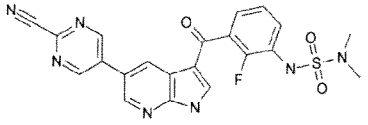
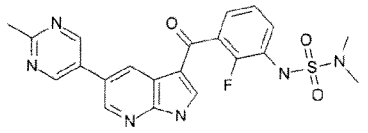
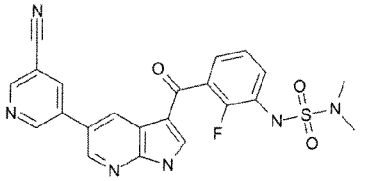
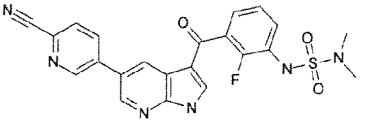
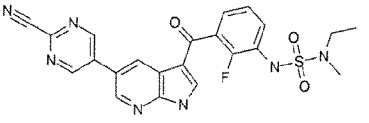
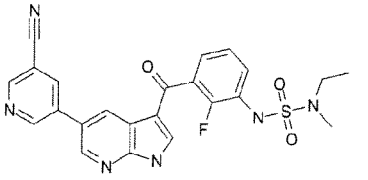
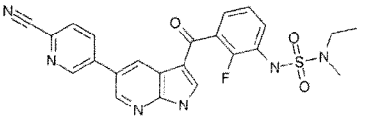
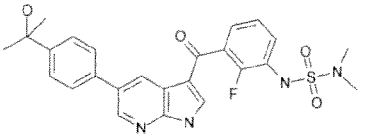
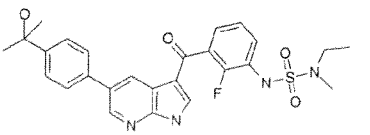
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P-0045		480.5
P-0046		509.6
P-0047		509.0
P-0048		507.0
P-0049		520.0
P-0050		530.0
P-0051		483.1
P-0052		481.0
P-0053		508.0

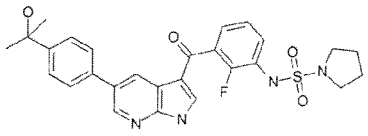
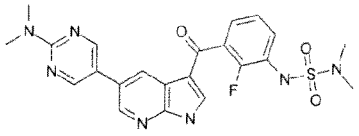
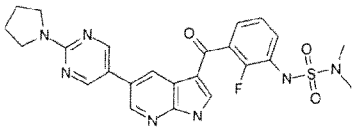
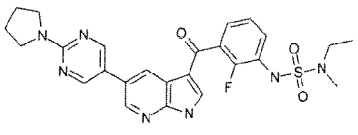
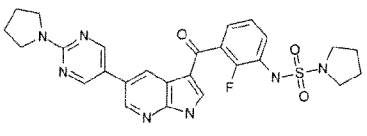
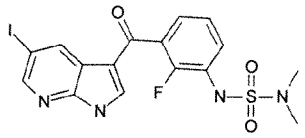
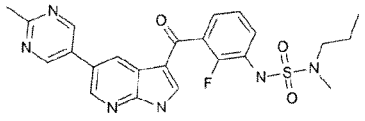
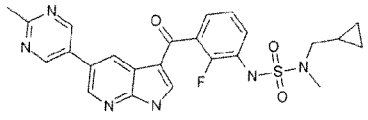
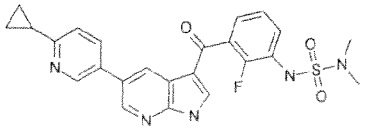
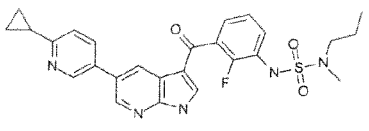
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P-0055		504.1
P-0056		469.0
P-0057		497.0
P-0058		495.0
P-0059		522.0
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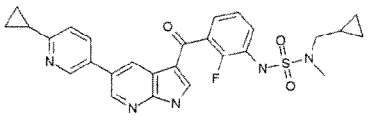
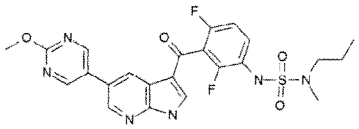
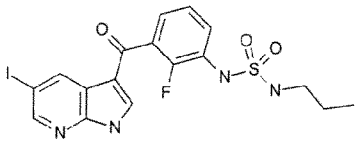
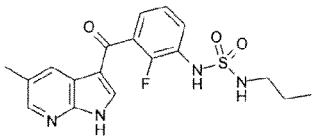
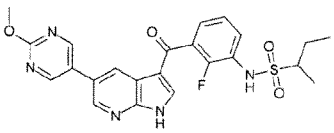
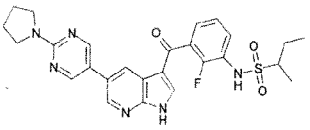
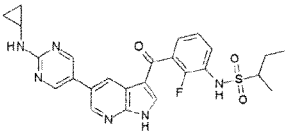
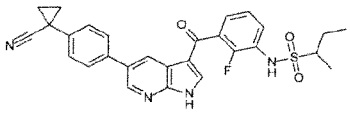
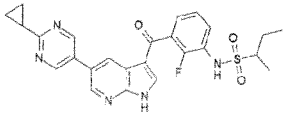
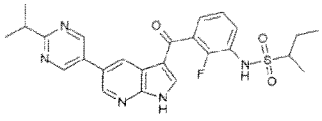
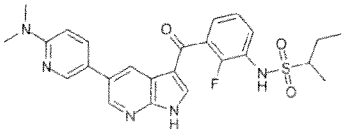
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P-0067		468.0
P-0068		471.0
P-0069		489.0
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P-0071		503.1
P-0072		513.5
P-0073		515.1
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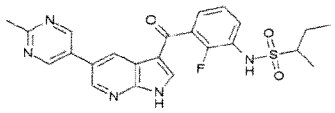
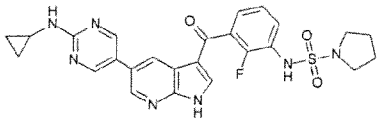
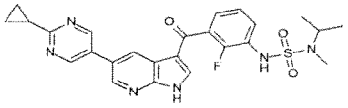
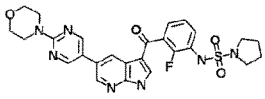
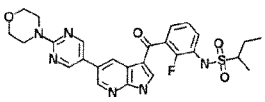
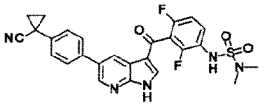
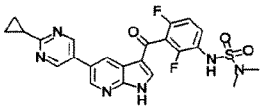
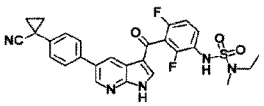
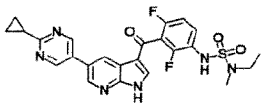
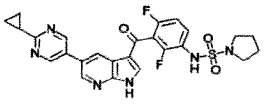
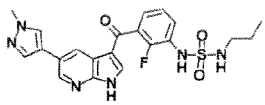
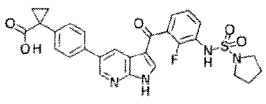
P-0075		499.0
P-0076		497.1
P-0077		510.5
P-0078		527.1
P-0079		550.0
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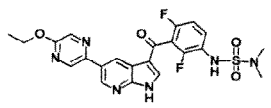
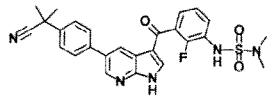
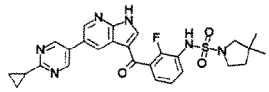
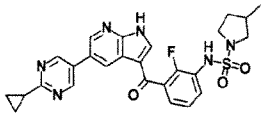
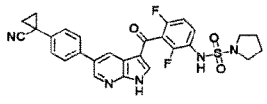
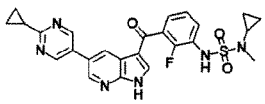
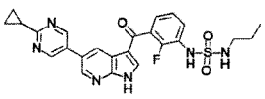
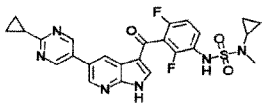
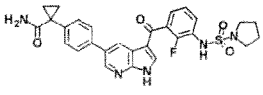
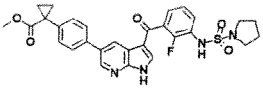
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P-0086		509.1
P-0087		494.2
P-0088		519.5
P-0089		461.1
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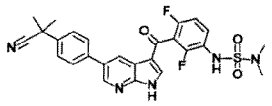
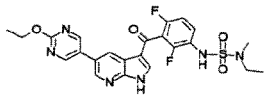
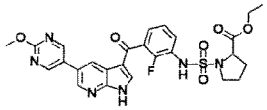
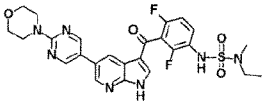
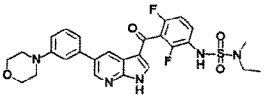
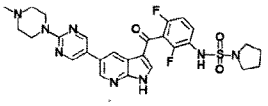
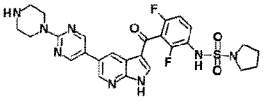
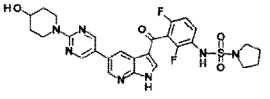
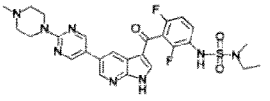
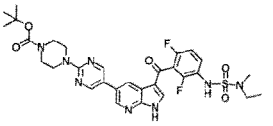
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P-0098		465.4
P-0099		465.5
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P-0101		479.5
P-0102		479.0
P-0103		497.5
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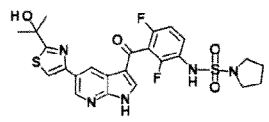
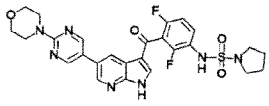
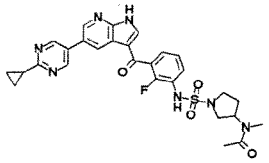
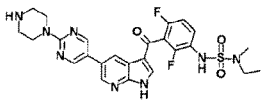
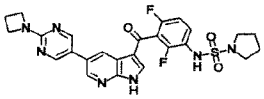
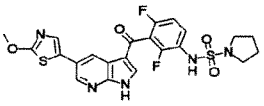
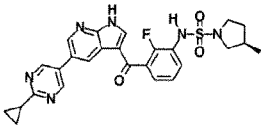
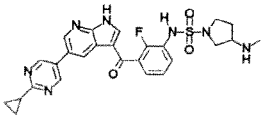
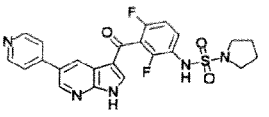
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P-0106		484.5
P-0107		510.6
P-0108		524.6
P-0109		536.6
P-0110		489.3
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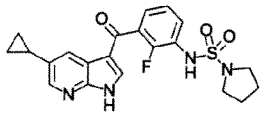
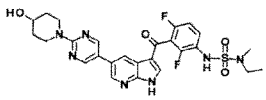
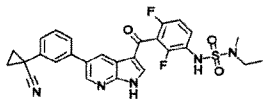
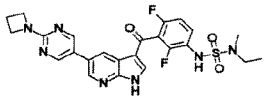
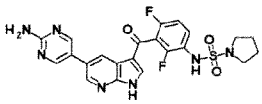
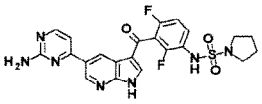
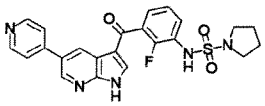
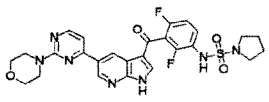
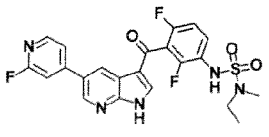
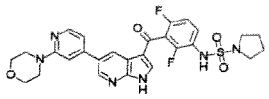
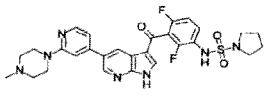
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P-0116		517.5
P-0117		503.0
P-0223		391.4
P-0224		484.5
P-0225		523.6
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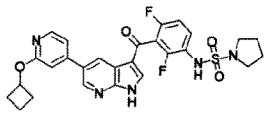
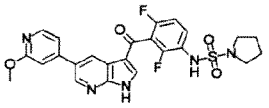
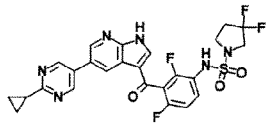
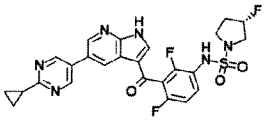
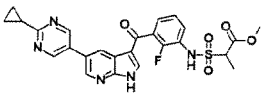
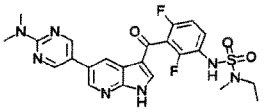
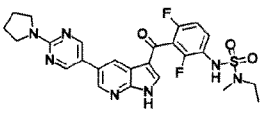
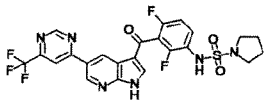
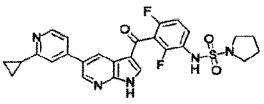
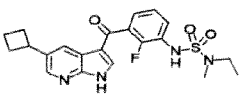
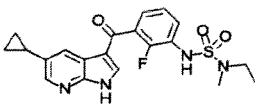
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P-0232		522.6
P-0233		509.6
P-0235		552.5
P-0236		539.4
P-0237		522.5
P-0238		499.5
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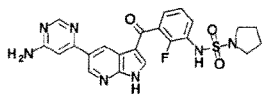
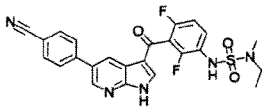
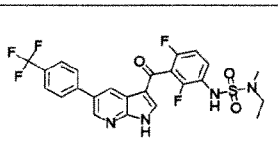
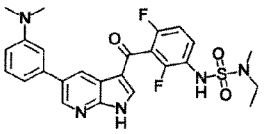
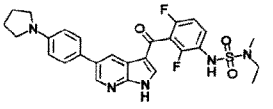
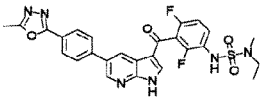
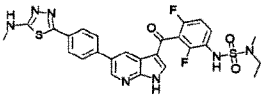
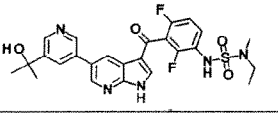
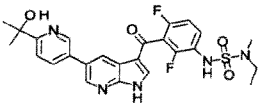
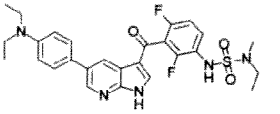
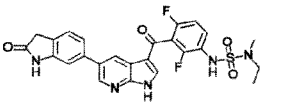
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P-0248		548.5
P-0249		507.5
P-0251		495.5
P-0252		525.5
P-0253		548.6
P-0254		563.5

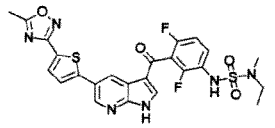
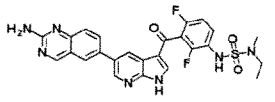
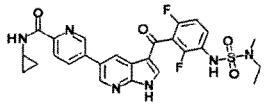
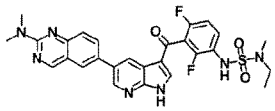
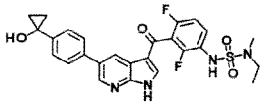
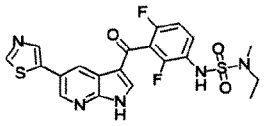
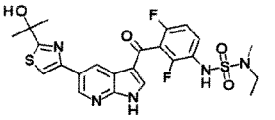
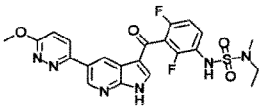
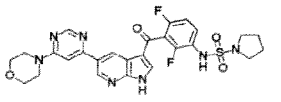
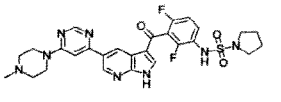
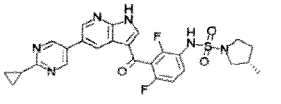
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P-0256		517.2
P-0257		569.6
P-0258		558.5
P-0259		556.6
P-0260		583.6
P-0261		569.4
P-0262		584.5
P-0263		571.6
P-0264		657.7

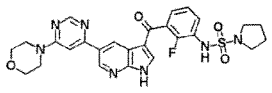
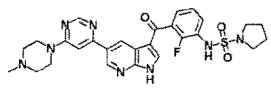
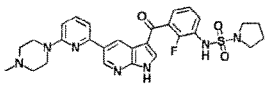
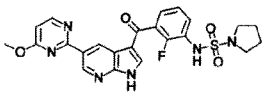
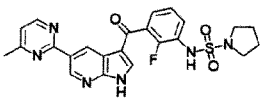
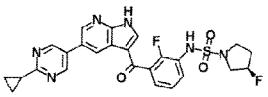
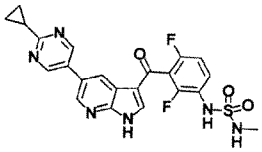
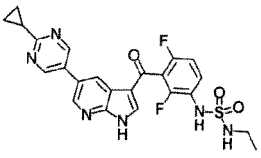
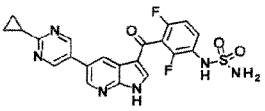
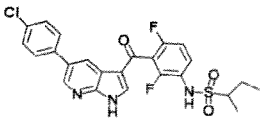
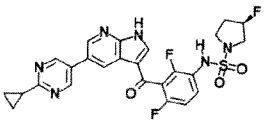
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P-0266		570.5
P-0267		578.6
P-0268		557.5
P-0269		540.5
P-0270		520.6
P-0271		521.5
P-0272		536.6
P-0273		484.4

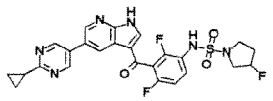
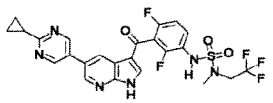
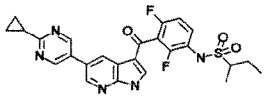
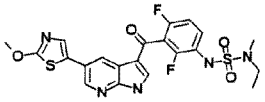
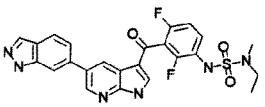
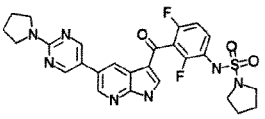
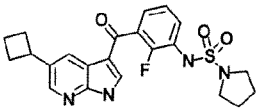
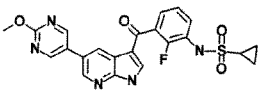
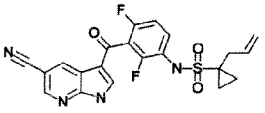
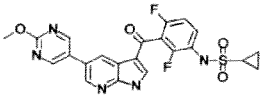
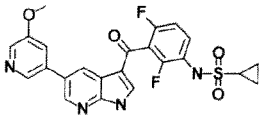
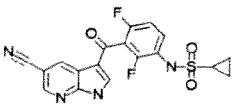
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P-0275		572.6
P-0276		536.5
P-0277		528.5
P-0279		500.3
P-0280		500.5
P-0281		466.5
P-0282		570.6
P-0283		490.4
P-0284		569.6
P-0285		582.5

P-0286		554.6
P-0287		514.5
P-0288		561.5
P-0289		543.4
P-0291		524.2
P-0292		516.2
P-0293		542.5
P-0294		553.5
P-0295		524.6
P-0297		431.5
P-0298		417.4

P-0299		482.5
P-0300		496.5
P-0301		539.4
P-0302		514.6
P-0303		540.5
P-0304		553.6
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P-0308		542.5
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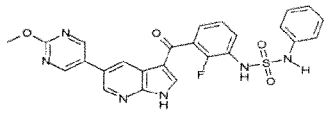
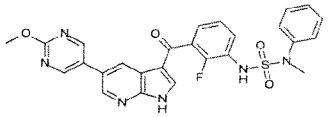
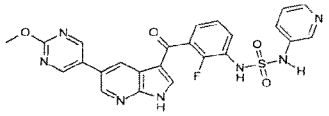
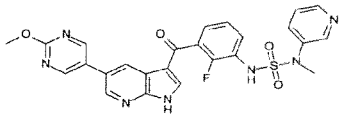
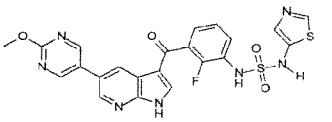
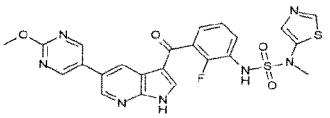
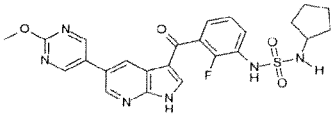
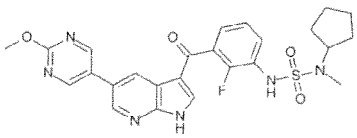
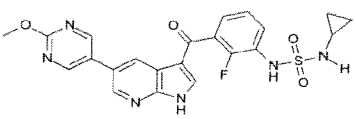
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P-0311		538.5
P-0312		555.4
P-0313		566.6
P-0314		527.5
P-0315		478.5
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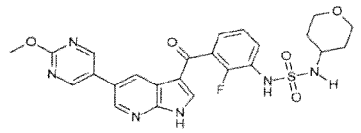
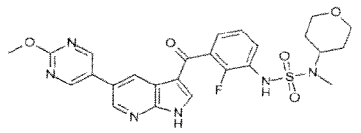
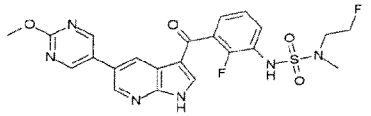
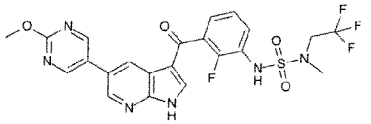
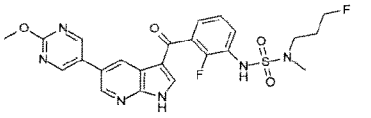
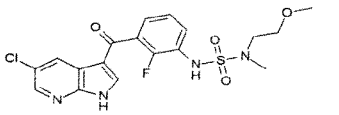
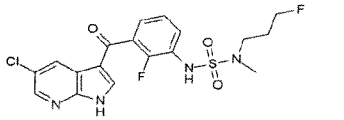
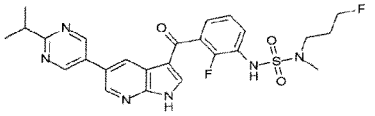
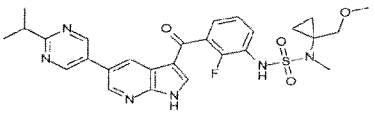
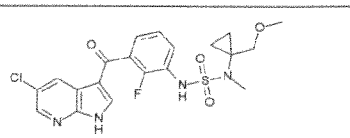
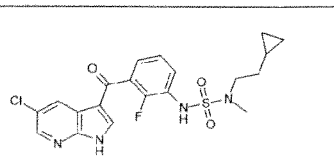
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P-0322		565.5
P-0324		564.8
P-0325		497.5
P-0326		481.4
P-0327		525.5
P-0334		485.4
P-0335		499.5
P-0336		471.4
P-0337		504.0
P-0338		542.9

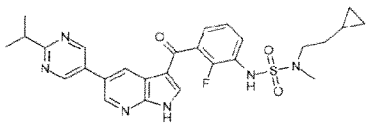
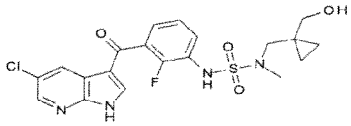
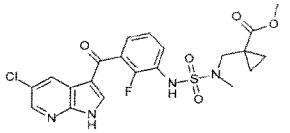
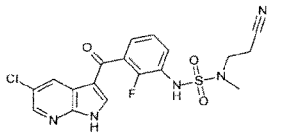
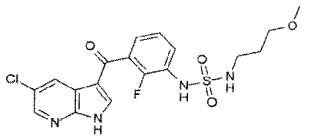
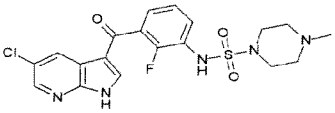
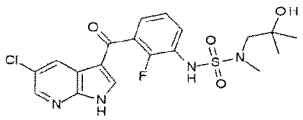
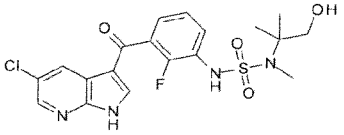
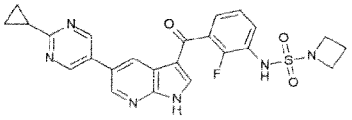
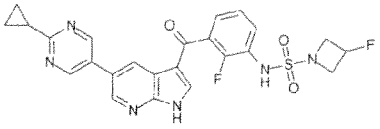
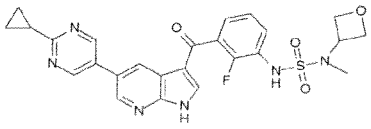
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P-0340		567.5
P-0342		512.5
P-0343		507.5401
P-0344		511.5
P-0345		554.6
P-0346		443.5
P-0347		468.4
P-0348		443.4
P-0349		486.4
P-0350		485.5
P-0351		403.3

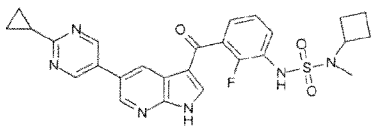
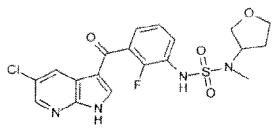
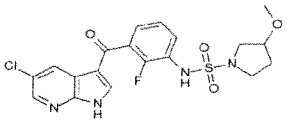
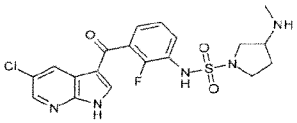
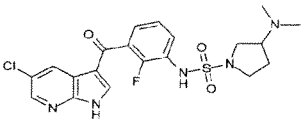
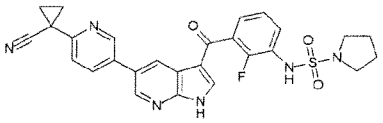
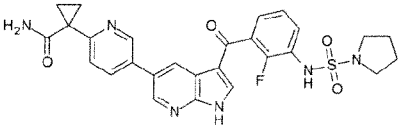
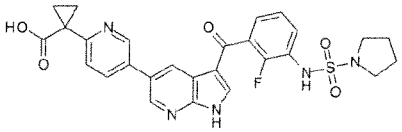
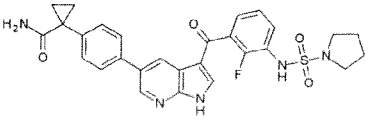
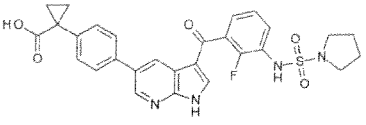
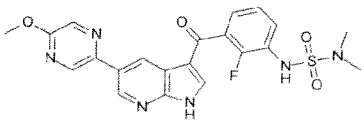
[0206] The following compounds are also prepared according to the protocols set forth in Examples 1, 2 and 4-9 and Schemes 1, 2 and 4-9. The data from the ^{1}H NMR and mass spectroscopies are consistent with the structures of the compounds.

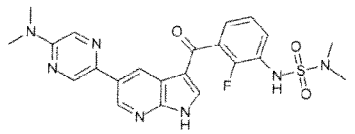
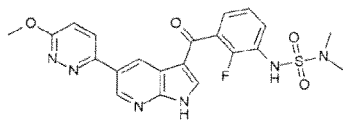
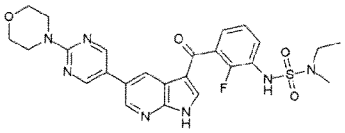
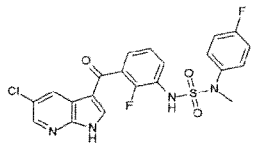
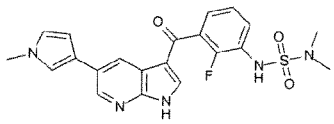
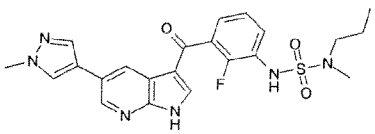
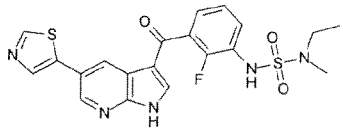
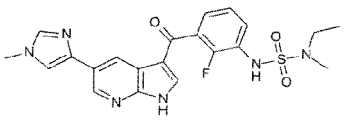
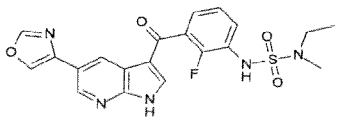
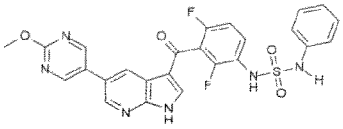
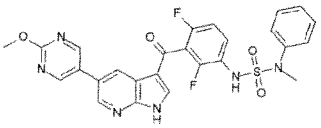
Table 3

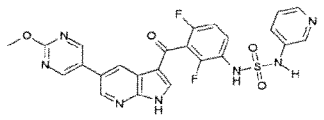
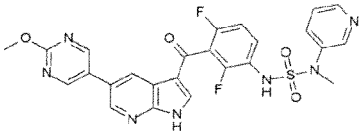
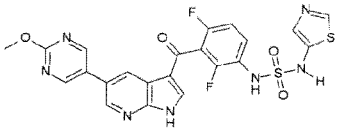
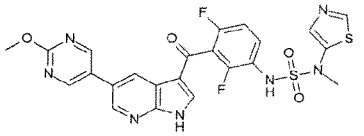
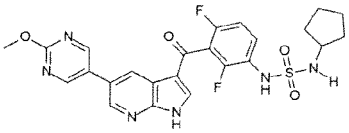
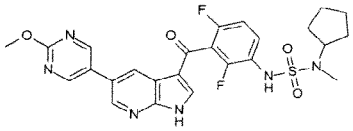
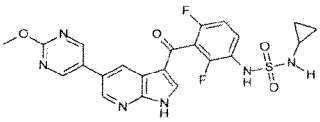
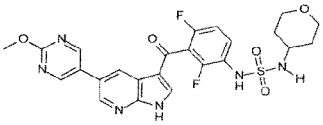
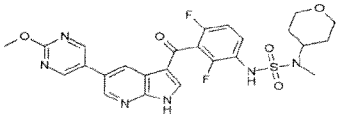
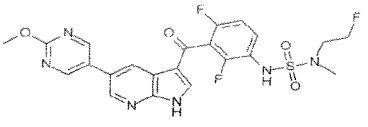
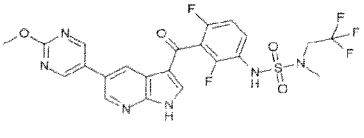
Compound No.	Name (MS(ESI) $[M+H^+]^+$)	Structure
P-0118	[2-fluoro-3-(phenylsulfamoylamino)phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (519.1)	
P-0119	3-[2-fluoro-3-[[methyl(phenyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (533.1)	
P-0120	[2-fluoro-3-(3-pyridylsulfamoylamino)phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (520.1)	
P-0121	3-[2-fluoro-3-[[methyl(3-pyridyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (534.1)	
P-0122	[2-fluoro-3-(thiazol-5-ylsulfamoylamino)phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (526.1)	
P-0123	5-[[2-fluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]sulfamoyl-methyl-amino]thiazole (540.1)	
P-0124	[3-(cyclopentylsulfamoylamino)-2-fluoro-phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (511.1)	
P-0125	3-[3-[[cyclopentyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (525.2)	
P-0126	[3-(cyclopropylsulfamoylamino)-2-fluoro-phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (483.1)	

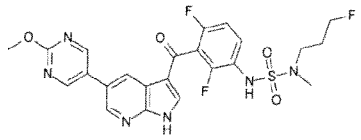
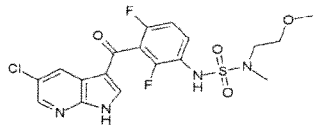
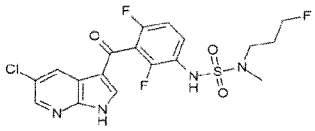
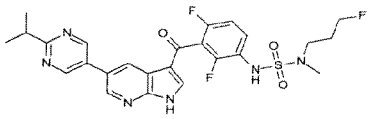
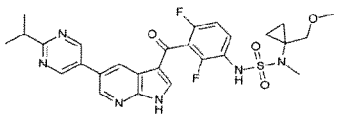
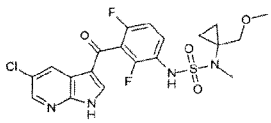
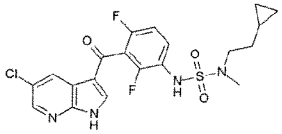
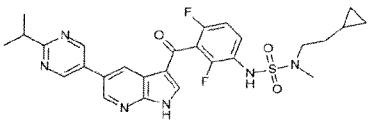
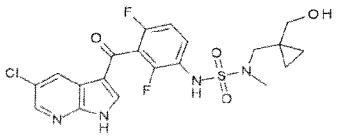
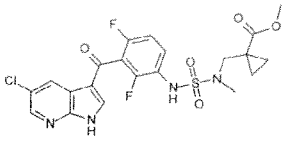
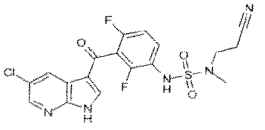
P-0127	[2-fluoro-3-(tetrahydropyran-4-ylsulfamoylamino)phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (527.1)	
P-0128	3-[2-fluoro-3-[[methyl(tetrahydropyran-4-yl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (541.2)	
P-0129	3-[2-fluoro-3-[[2-fluoroethyl(methyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (503.1)	
P-0130	3-[2-fluoro-3-[[methyl(2,2,2-trifluoroethyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (539.1)	
P-0131	3-[2-fluoro-3-[[3-fluoropropyl(methyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (517.1)	
P-0132	5-chloro-3-[2-fluoro-3-[[2-methoxyethyl(methyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (441.1)	
P-0133	5-chloro-3-[2-fluoro-3-[[3-fluoropropyl(methyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (443.1)	
P-0134	3-[2-fluoro-3-[[3-fluoropropyl(methyl)sulfamoyl]amino]benzoyl]-5-(2-isopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (529.2)	
P-0135	3-[2-fluoro-3-[[[1-(methoxymethyl)cyclopropyl]-methyl-sulfamoyl]amino]benzoyl]-5-(2-isopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (553.2)	
P-0136	5-chloro-3-[2-fluoro-3-[[[1-(methoxymethyl)cyclopropyl]-methyl-sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (467.1)	
P-0137	5-chloro-3-[3-[[2-cyclopropylethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (451.1)	

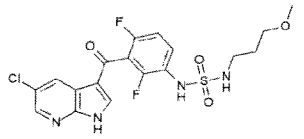
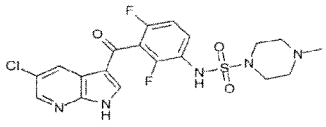
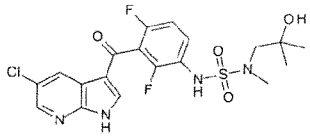
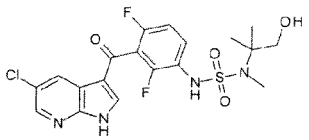
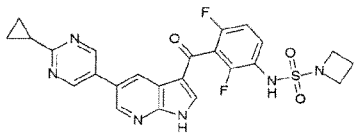
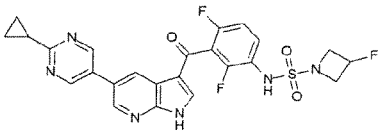
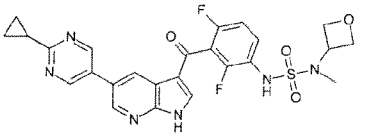
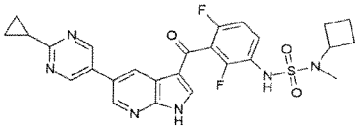
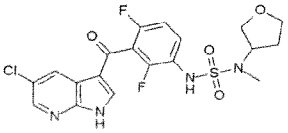
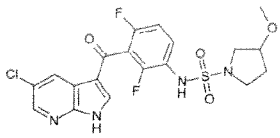
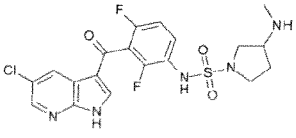
P-0138	3-[3-[[2-cyclopropylethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-isopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (537.2)	
P-0139	5-chloro-3-[2-fluoro-3-[[[1-(hydroxymethyl)cyclopropyl]methyl-methyl-sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (467.1)	
P-0140	methyl 1-[[[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]sulfamoyl-methyl-amino]methyl]cyclopropanecarboxylate (495.1)	
P-0141	5-chloro-3-[3-[[2-cyanoethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (436.1)	
P-0142	(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-fluoro-3-(3-methoxypropylsulfamoylamino)phenyl]methanone (441.1)	
P-0143	N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-4-methyl-piperazine-1-sulfonamide (452.1)	
P-0144	5-chloro-3-[2-fluoro-3-[[(2-hydroxy-2-methyl-propyl)-methyl-sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (455.1)	
P-0145	5-chloro-3-[2-fluoro-3-[[(2-hydroxy-1,1-dimethyl-ethyl)-methyl-sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (455.1)	
P-0146	N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]azetidine-1-sulfonamide (493.1)	
P-0147	N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]-3-fluoro-azetidine-1-sulfonamide (511.1)	
P-0148	5-(2-cyclopropylpyrimidin-5-yl)-3-[2-fluoro-3-[[methyl(oxetan-3-yl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (523.1)	

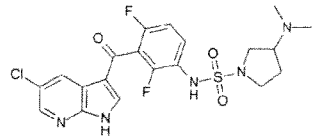
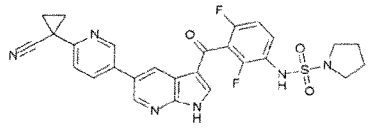
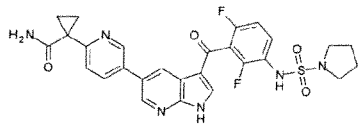
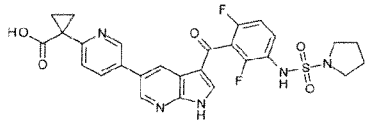
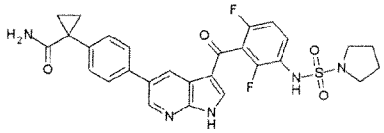
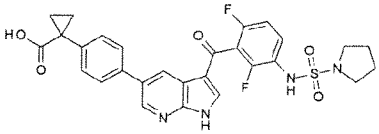
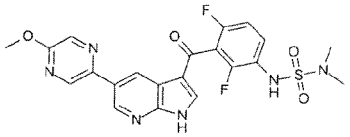
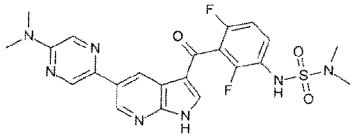
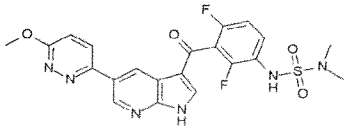
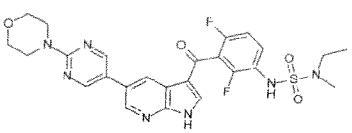
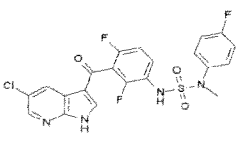
P-0149	3-[3-[[cyclobutyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (521.2)	
P-0150	5-chloro-3-[2-fluoro-3-[[methyl(tetrahydrofuran-3-yl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (453.1)	
P-0151	N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-3-methoxy-pyrrolidine-1-sulfonamide (453.1)	
P-0152	N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-3-(methylamino)pyrrolidine-1-sulfonamide (452.1)	
P-0153	N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-3-(dimethylamino)pyrrolidine-1-sulfonamide (466.1)	
P-0154	N-[3-[5-[6-(1-cyanocyclopropyl)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide (531.2)	
P-0155	1-[5-[3-[2-fluoro-3-(pyrrolidin-1-ylsulfonylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]cyclopropanecarboxamide (549.2)	
P-0156	1-[5-[3-[2-fluoro-3-(pyrrolidin-1-ylsulfonylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]cyclopropanecarboxylic acid (550.2)	
P-0157	1-[4-[3-[2-fluoro-3-(pyrrolidin-1-ylsulfonylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]cyclopropanecarboxamide (548.2)	
P-0158	1-[4-[3-[2-fluoro-3-(pyrrolidin-1-ylsulfonylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]cyclopropanecarboxylic acid (548.2)	
P-0159	3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-(5-methoxypyrazin-2-yl)-1H-pyrrolo[2,3-b]pyridine (471.1)	

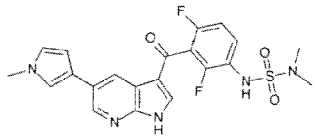
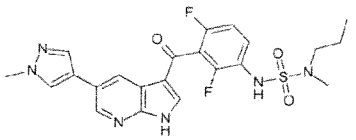
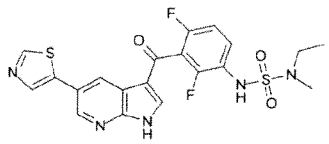
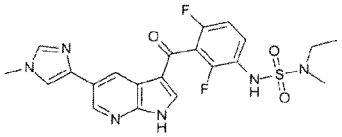
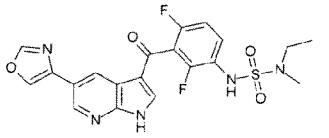
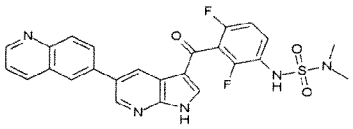
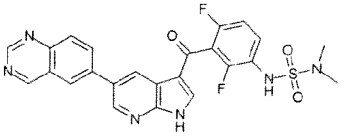
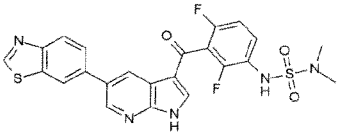
P-0160	5-[5-(dimethylamino)pyrazin-2-yl]-3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (484.2)	
P-0161	3-[3-(dimethylsulfamoylamino)-2-fluoro-benzoyl]-5-(6-methoxypyridazin-3-yl)-1H-pyrrolo[2,3-b]pyridine (471.1)	
P-0162	4-[5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyrimidin-2-yl]morpholine (540.2)	
P-0163	5-chloro-3-[2-fluoro-3-[[(4-fluorophenyl)-methyl-sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (477.1)	
P-0164	3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(1-methylpyrrol-3-yl)-1H-pyrrolo[2,3-b]pyridine (442.1)	
P-0165	3-[2-fluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-5-(1-methylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (471.2)	
P-0166	5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]thiazole (460.1)	
P-0167	3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-5-(1-methylimidazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (457.1)	
P-0168	4-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]oxazole (444.1)	
P-0169	[2,6-difluoro-3-(phenylsulfamoylamino)phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (537.1)	
P-0170	3-[2,6-difluoro-3-[[methyl(phenyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (551.1)	

P-0171	[2,6-difluoro-3-(3-pyridylsulfamoylamino)phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (538.1)	
P-0172	3-[2,6-difluoro-3-[[methyl(3-pyridyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (552.1)	
P-0173	[2,6-difluoro-3-(thiazol-5-ylsulfamoylamino)phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (544.1)	
P-0174	5-[[2,4-difluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]sulfamoyl-methyl-amino]thiazole (558.1)	
P-0175	[3-(cyclopentylsulfamoylamino)-2,6-difluoro-phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (529.1)	
P-0176	3-[3-[[cyclopentyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (543.2)	
P-0177	[3-(cyclopropylsulfamoylamino)-2,6-difluoro-phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (501.1)	
P-0178	[2,6-difluoro-3-(tetrahydropyran-4-ylsulfamoylamino)phenyl]-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (545.1)	
P-0179	3-[2,6-difluoro-3-[[methyl(tetrahydropyran-4-yl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (559.1)	
P-0180	3-[2,6-difluoro-3-[[2-fluoroethyl(methyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (521.1)	
P-0181	3-[2,6-difluoro-3-[[methyl(2,2,2-trifluoroethyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (556.1)	

P-0182	3-[2,6-difluoro-3-[[3-fluoropropyl(methyl)sulfamoyl]amino]benzoyl]-5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (534.1)	
P-0183	5-chloro-3-[2,6-difluoro-3-[[2-methoxyethyl(methyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (458.1)	
P-0184	5-chloro-3-[2,6-difluoro-3-[[3-fluoropropyl(methyl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (561.1)	
P-0185	3-[2,6-difluoro-3-[[3-fluoropropyl(methyl)sulfamoyl]amino]benzoyl]-5-(2-isopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (547.2)	
P-0186	3-[2,6-difluoro-3-[[[1-(methoxymethyl)cyclopropyl]-methyl-sulfamoyl]amino]benzoyl]-5-(2-isopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (571.2)	
P-0187	5-chloro-3-[2,6-difluoro-3-[[[1-(methoxymethyl)cyclopropyl]-methyl-sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (485.1)	
P-0188	5-chloro-3-[3-[[2-cyclopropylethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (469.1)	
P-0189	3-[3-[[2-cyclopropylethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(2-isopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (555.2)	
P-0190	5-chloro-3-[2,6-difluoro-3-[[[1-(hydroxymethyl)cyclopropyl]methyl-methyl-sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (485.1)	
P-0191	methyl 1-[[[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]sulfamoyl-methyl-amino]methyl]cyclopropanecarboxylate (513.1)	
P-0192	5-chloro-3-[3-[[2-cyanoethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (454.0)	

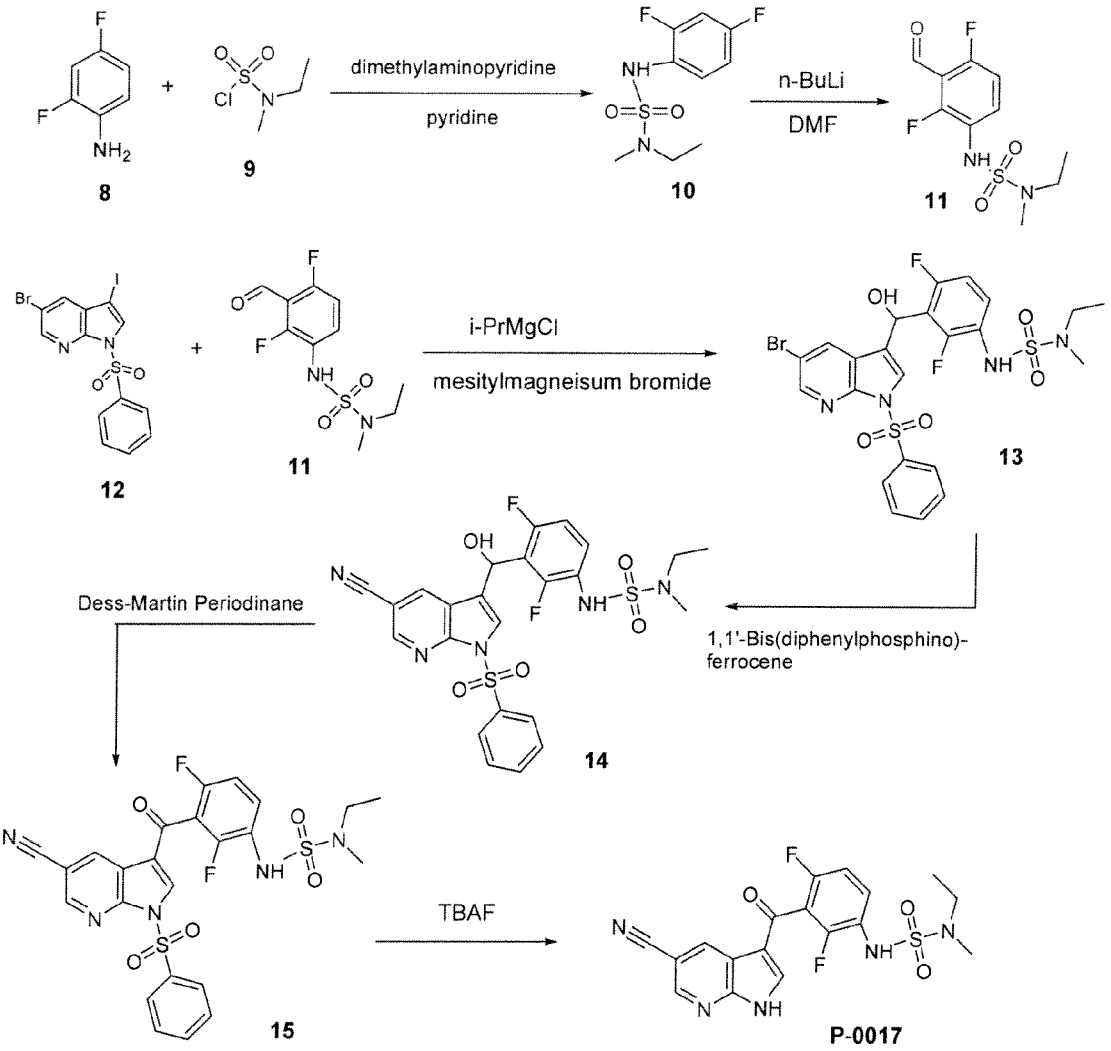
P-0193	(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2,6-difluoro-3-(3-methoxypropylsulfamoylamino)phenyl]methanone (459.1)	
P-0194	N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-methyl-piperazine-1-sulfonamide (470.1)	
P-0195	5-chloro-3-[2,6-difluoro-3-[[(2-hydroxy-2-methyl-propyl)-methyl-sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (473.1)	
P-0196	5-chloro-3-[2,6-difluoro-3-[[(2-hydroxy-1,1-dimethyl-ethyl)-methyl-sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (473.1)	
P-0197	N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]azetidine-1-sulfonamide (511.1)	
P-0198	N-[3-[5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]-3-fluoro-azetidine-1-sulfonamide (529.1)	
P-0199	5-(2-cyclopropylpyrimidin-5-yl)-3-[2,6-difluoro-3-[[methyl(oxetan-3-yl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (541.1)	
P-0200	3-[3-[[cyclobutyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine (539.2)	
P-0201	5-chloro-3-[2,6-difluoro-3-[[methyl(tetrahydrofuran-3-yl)sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (471.1)	
P-0202	N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-methoxy-pyrrolidine-1-sulfonamide (471.1)	
P-0203	N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-(methylamino)pyrrolidine-1-sulfonamide (470.1)	

P-0204	N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-(dimethylamino)pyrrolidine-1-sulfonamide (484.1)	
P-0205	N-[3-[5-[6-(1-cyanocyclopropyl)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide (549.1)	
P-0206	1-[5-[3-[2,6-difluoro-3-(pyrrolidin-1-ylsulfonylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]cyclopropanecarboxamide (567.2)	
P-0207	1-[5-[3-[2,6-difluoro-3-(pyrrolidin-1-ylsulfonylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]cyclopropanecarboxylic acid (568.1)	
P-0208	1-[4-[3-[2,6-difluoro-3-(pyrrolidin-1-ylsulfonylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]cyclopropanecarboxamide (566.2)	
P-0209	1-[4-[3-[2,6-difluoro-3-(pyrrolidin-1-ylsulfonylamino)benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl]cyclopropanecarboxylic acid (567.1)	
P-0210	3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-5-(5-methoxypyrazin-2-yl)-1H-pyrrolo[2,3-b]pyridine (489.1)	
P-0211	5-[5-(dimethylamino)pyrazin-2-yl]-3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (502.1)	
P-0212	3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-5-(6-methoxypyridazin-3-yl)-1H-pyrrolo[2,3-b]pyridine (489.1)	
P-0213	4-[5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyrimidin-2-yl]morpholine (558.2)	
P-0214	5-chloro-3-[2,6-difluoro-3-[[(4-fluorophenyl)-methyl-sulfamoyl]amino]benzoyl]-1H-pyrrolo[2,3-b]pyridine (495.0)	

P-0215	3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-5-(1-methylpyrrol-3-yl)-1H-pyrrolo[2,3-b]pyridine (460.1)	
P-0216	3-[2,6-difluoro-3-[[methyl(propyl)sulfamoyl]amino]benzoyl]-5-(1-methylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (489.1)	
P-0217	5-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]thiazole (478.1)	
P-0218	3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-5-(1-methylimidazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (475.1)	
P-0219	4-[3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]oxazole (462.1)	
P-0220	6-[3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]quinoline (508.1)	
P-0221	6-[3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]quinazoline (509.1)	
P-0222	6-[3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-1,3-benzothiazole (514.1)	

Example 3: Preparation of 5-cyano-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (P-0017).

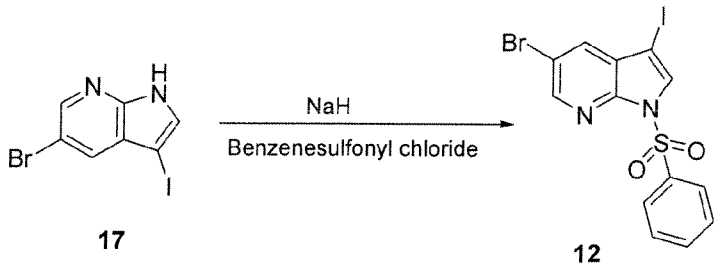
Scheme 3



[0207] Synthesis of 1-[(ethyl(methyl)sulfamoyl)amino]-2,4-difluoro-benzene (10): To a solution of 2,4-Difluoroaniline (2.21 g, 17.13 mmol) in dichloroethane (10 mL) were added 4-Dimethylaminopyridine (0.1 g, 0.82 mmol), N-ethyl-N-methyl-sulfamoyl chloride (2.7 g, 17.13 mmol) and pyridine (2 g, 25.28 mmol). The mixture was stirred at room temperature overnight. The resulting mixture was poured into an aqueous potassium carbonate solution, and extracted with ethyl acetate (EtOAc). The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography using 20% to 100% ethyl acetate in hexane as an eluent to give th desired product (**10**, 3.08 g, 71.8% yield). MS (ESI) $[M+H^+]^+ = 250.8$. ^1H NMR spectrum is consistent with the structure of the compound.

[0208] Synthesis of 1-[(ethyl(methyl)sulfamoyl)amino]-2,4-difluoro-3-formyl-benzene (11): To a mixture of 1-[(ethyl(methyl)sulfamoyl)amino]-2,4-difluoro-benzene (**10**, 3.08 g, 12.31 mmol) in tetrahydrofuran (THF) (25.0 mL) under an atmosphere of nitrogen at -78 °C was added 2.5M n-butyllithium (n-BuLi) in THF (5 mL). The colorless reaction mixture was kept at -78 °C for one hour and 2.5M n-BuLi in THF (5.4 ml) was added to the reaction mixture. The reaction was kept at -78 °C for 1 hr and added N,N-Dimethylformamide (DMF) (1.8 mL, 23.25 mmol). The reaction mixture turned into solid. The solid reaction mixture was shaken for about 5 minutes to obtain a slurry. The reaction mixture was kept in a dry ice-acetone bath for 1 hr and was allowed to warm up to room temperature for 1 hour. The reaction mixture was poured into an aqueous ammonia chloride solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified with silica gel column chromatography using 30% to 100% ethyl acetate in hexane as an eluent to give the desired product (**11**, 1.10 g, 32.1% yield). MS (ESI) $[M+H^+]^+ = 278.8$. ^1H NMR spectrum is consistent with the structure of the compound.

[0209] Synthesis of 1-(benzenesulfonyl)-5-bromo-3-iodo-pyrrolo[2,3-b]pyridine (12).



17 **12**

[0210] To a solution of 5-bromo-3-iodo-1H-pyrrolo[2,3-b]pyridine (2.7 g, 8.36 mmol) in DMF (30.0 mL) was added sodium hydride (60%, 0.37 g, 9.2 mmol) at room temperature. After 10 minutes, benzenesulfonyl chloride (1.13 ml, 8.78 mmol) was added to and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was poured in to water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated, filtered and washed with ethyl acetate to obtain the desired product **12** as a white solid (2.70 g). The mother liquid was purified with silica gel column chromatography using 20% to 100% ethyl acetate in hexane as an eluent to give addition product (0.90 g). The combined yield is 93.0%. MS (ESI) $[M+H^+]^+ = 464.1$. ^1H NMR spectrum is consistent with the structure of the compound.

[0211] Synthesis of 1-(benzenesulfonyl)-5-bromo-3-[[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-phenyl]-hydroxy-methyl]pyrrolo[2,3-b]pyridine (13):

Step 1: To a solution of 1-[[ethyl(methyl)sulfamoyl]amino]-2,4-difluoro-3-formyl-benzene (**11**, 0.76 g, 2.73 mmol) in THF (5 mL), under nitrogen at -78 °C, was added 1M mesitylmagnesium bromide in THF (2.8 ml). The reaction solution was stirred for 40 minutes.

Step 2: To 1-(benzenesulfonyl)-5-bromo-3-iodo-pyrrolo[2,3-b]pyridine (**17**, 1.76 g, 3.79 mmol) in THF (10 mL), under an atmosphere of nitrogen at -40 °C, was added a solution of i-PrMgCl (2.0 M in THF, 1.9 mL). The reaction mixture was allowed to warm up to 5 °C in 1 hour. The reaction mixture was cooled to -40 °C and added the reaction solution from step 1. The resulting reaction mixture was allowed to warm to room temperature in 1 hr, poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel column chromatography using 20% to 100% ethyl acetate in hexane as an eluent to give the desired product (**13**, 1.10g, 65.4%). MS (ESI) $[M+H^+]^+$ = 614.7 and 616.7. ^{1}H NMR spectrum is consistent with the structure of the compound.

[0212] Synthesis of 1-(benzenesulfonyl)-5-cyano-3-[[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-phenyl]-hydroxy-methyl]pyrrolo[2,3-b]pyridine (14): To 1-(benzenesulfonyl)-5-bromo-3-[[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-phenyl]-hydroxy-methyl]pyrrolo[2,3-b]pyridine (**13**, 500 mg, 0.81 mmol) were added zinc cyanide (0.05 ml, 0.77 mmol), zinc, tris(dibenzylideneacetone)dipalladium(0) (90 mg, 0.09 mmol), 1,1'-Bis(diphenylphosphino)ferrocene (90 mg, 0.16 mmol), and DMF (10 ml) under nitrogen. The reaction mixture was heated to 120 °C overnight. The resulting reaction mixture was poured into an aqueous potassium carbonate solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated and purified with silica gel column chromatography using 20% to 100% ethyl acetate in hexane as an eluent to give the desired product (**14**, 0.20 g, 43.8% yield). MS (ESI) $[M+H^+]^+$ = 562.0. ^{1}H NMR spectrum is consistent with the structure of the compound.

[0213] Synthesis of 1-(benzenesulfonyl)-5-cyano-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]pyrrolo[2,3-b]pyridine (15): To 1-(benzenesulfonyl)-5-cyano-3-[[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-phenyl]-hydroxy-methyl]pyrrolo[2,3-b]pyridine (**14**, 0.2 g, 0.36 mmol) in methylene chloride (10 mL) was added Dess-Martin Periodinane (0.18 g, 0.43 mmol). The reaction mixture was stirred at room temperature for 20 minutes. The reaction mixture was concentrated, and purified by silica gel column chromatography using 25% to 100% ethyl acetate in hexane as an eluent to give th desired product (**15**, 170 mg, 85.3% yield). MS (ESI) $[M+H^+]^+$ = 560.5. ^{1}H NMR spectrum is consistent with the structure of the compound.

[0214] Synthesis of 5-cyano-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine (P-0017): To 1-(benzenesulfonyl)-5-cyano-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]pyrrolo[2,3-b]pyridine (**15**, 0.17 g, 0.3 mmol) in THF (10 mL) was added tetra-n-butylamonium fluoride (TBAF) (0.19 g, 0.61 mmol). The reaction mixture was stirred at room temperature overnight. The resulting reaction mixture was poured into an aqueous ammonia chloride solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated and purified by silica

gel column chromatography using 2% to 10% methanol in methylene chloride as an eluent to give the product (**P-0017**, 74.5 mg, 58.5% yield). MS (ESI) $[M+H^+]^+ = 420.1$. ^1H NMR spectrum is consistent with the structure of the compound.

[0215] The following compounds were prepared according to the protocols set forth in Example 3 and Scheme 3.

5-chloro-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0012)**,

N-[2,4-difluoro-3-(5-fluoro-4-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide **(P-0013)**,

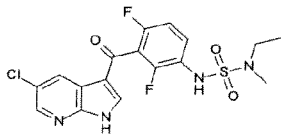
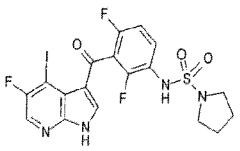
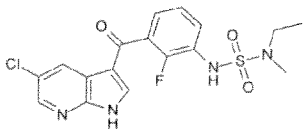
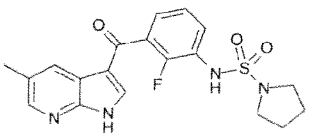
5-chloro-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0018)**,

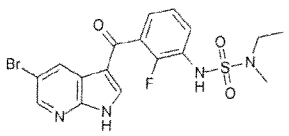
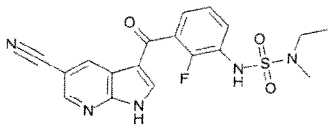
N-[2-fluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide **(P-0023)**,

5-bromo-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0038)**,

5-cyano-3-[3-[[ethyl(methyl)sulfamoyl]amino]-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **(P-0039)**.

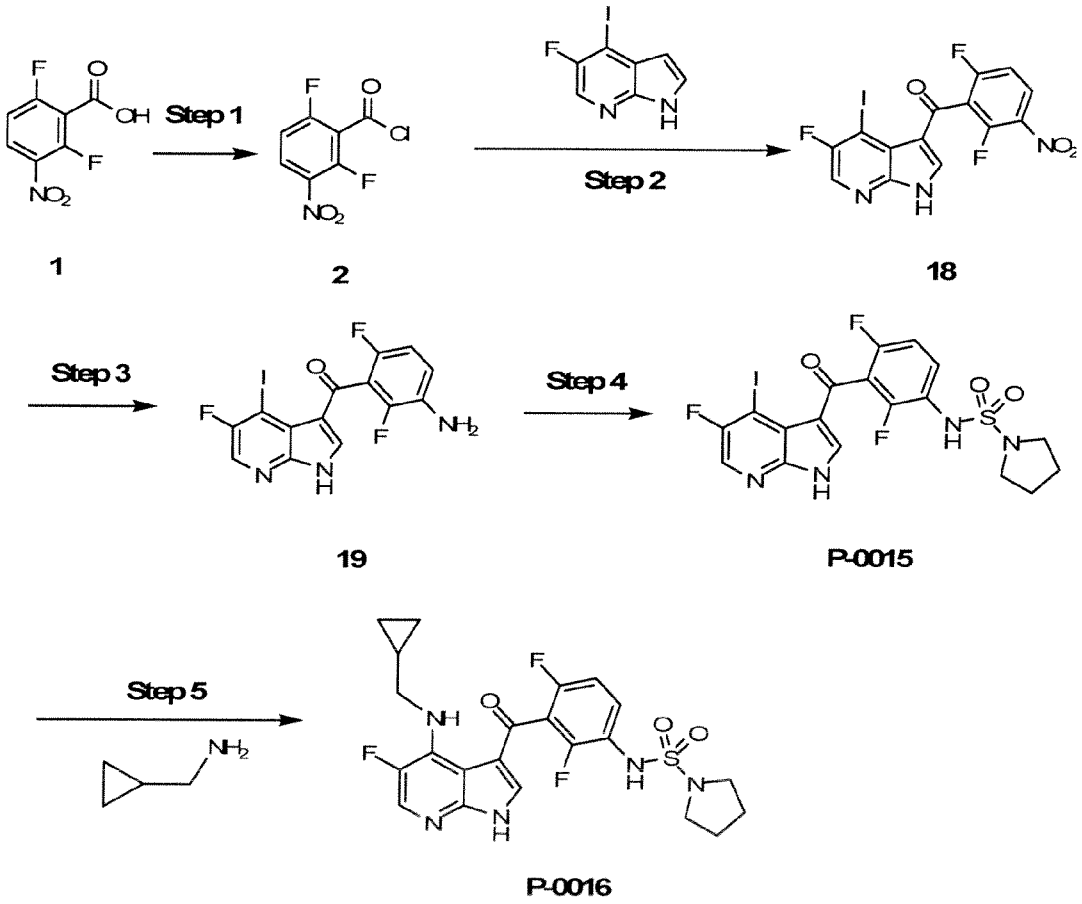
The following table provides structures of certain compounds of the present invention and observed mass. ^1H NMR spectra were consistent with the structures of the compounds.

	Compounds	MS(ESI) $[M+H^+]^+$ observed
P-0012		428.9
P-0015		551.1
P-0018		410.9
P-0023		402.9

P-0038		455.0
P-0039		454.9 and 456.9

Example 4: Preparation of N-[3-[4-(cyclopropylmethylamino)-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide (P-0016).

Scheme 4.



[0216] Step 1 –Synthessi of 2,6-difluoro-3-nitrobenzoyl chloride (2): In a round flask, 2,6-difluoro-3-nitrobenzoic acid (5.5 g, 0.03 mol) was added Thionyl chloride (20 mL, 0.27 mol) and N,N-Dimethylformamide (100 µl, 0.001 mol). The reaction mixture was placed in an oil bath at 80 °C for 4 hrs. All volatiles were removed and the residue was stripped from toluene twice and dried in high vacuo to give a yellow oily liquid (**2**, 5.95 g, 99%). It will be used as is.

[0217] Step 2 – Synthesis of (2,6-difluoro-3-nitro-phenyl)-(5-fluoro-4-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (18): In a Vial, 5-fluoro-4-iodo-1H-pyrrolo[2,3-b]pyridine (450 mg, 1.72 mmol) was cooled in an ice-water bath and added Trifluoromethanesulfonic acid (1.52 ml, 17.17 mmol). The reaction was stirred in an ice-water bath for 5 minutes and followed by adding 2,6-difluoro-3-nitrobenzoyl chloride (**2**, 500mg, 2.26 mmol). The resulting reaction mixture was stirred at an ice-water bath for 20 min and warmed up to room temperature. After 24 hrs at room temperature, the reaction mixture was quenched with 5 mL of methanol and stirred at r.t. for 1 hr. The mixture was poured to the saturated $NaHCO_3$ aqueous solution and extracted with EtOAc. The organic layer was washed with water and brine, dried with $MgSO_4$. The volatiles were removed under vacuo. The residue was suspended in acetonitrile and sonicated for 45 mins. The precipitate material was collected by filtration and washed with acetonitrile. The desired product (**18**, 532 mg, 69%) was a tan solid. MS (ESI) $[M+H^+]^+ = 447.8$.

[0218] Step 3 – Preparation of (3-amino-2,6-difluoro-phenyl)-(5-fluoro-4-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (19): In a round flask, (2,6-difluoro-3-nitro-phenyl)-(5-fluoro-4-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (0.53 g, 0.001 mol) was added EtOH (50 ml) and TIN(II) CHLORIDE (788 mg, 4.16 mmol). The reaction mixture was heated at 50 °C for over weekend. The reaction mixture treated with 50 mL of water and 50 mL saturated sodium bicarbonate. Additional ethyl acetate (20 mL) was added and the milky suspension was treated with celite and mixed well before filtering. The filtrate was added by brine to give clear layers that were separated. The organic layer was washed with water and brine and dried with MgSO4. The volatiles were removed under vacuum. The desired product was isolated by silica gel column chromatography (EtOAc/Hexane, 0-80% gradient) as an off-white solid (**19**, 365 mg, 73%). MS (ESI) $[M+H^+]^+ = 417.9$.

[0219] Step 4 – Preparation of N-[2,4-difluoro-3-(5-fluoro-4-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide (P-0015): In a round flask, (3-amino-2,6-difluoro-phenyl)-(5-fluoro-4-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (**19**, 180 mg, 0.43 mmol) was dissolved in 4 mL of THF and added PYRIDINE (106 µl, 1.29 mmol) and pyrrolidine-1-sulfonyl chloride (110 mg, 0.65 mmol). The solution was stirred at room temperature for about 90 hrs. The reaction mixture was added water and extracted with ethyl acetate. The organic layer was washed with water and brine and dried by MgSO4. The volatiles were removed under vacuum. The desired product was isolated by silica gel column chromatography (EtOAc/Hexane, 0-80% gradient) as a light yellow solid (**P-0015**, 99 mg, 41%). MS (ESI) $[M+H^+]^+ = 551.1$.

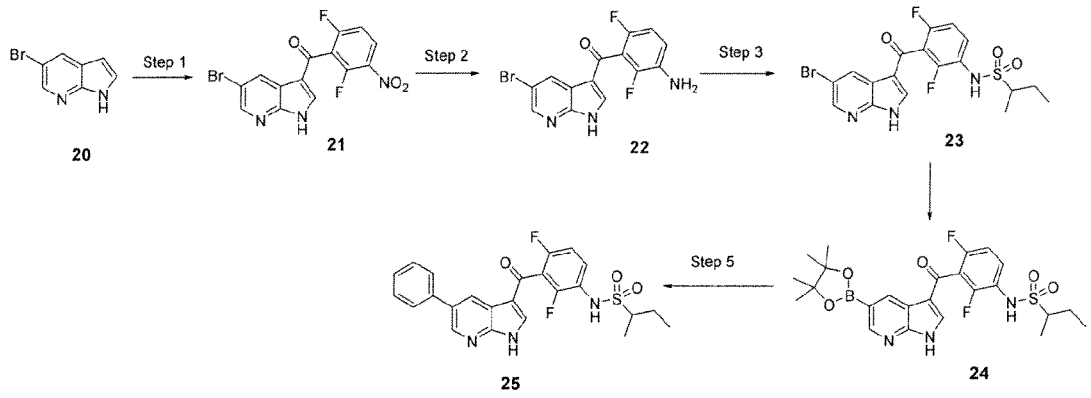
[0220] Step 5 – Preparation of N-[3-[4-(cyclopropylmethylamino)-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]pyrrolidine-1-sulfonamide (P-0016): To N-[2,4-difluoro-3-(5-fluoro-4-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]pyrrolidine-1-sulfonamide (95mg, 0.17 mmol) in isopropyl alcohol (2 ml) was added cyclopropylmethanamine (0.5 mL, 49.11mg, 0.69 mmol). The resulting solution was stirred at 90 °C overnight. The reaction mixture

was concentrated in vacuo and purified by silica gel on the companion with 8 g-cartridge using EtOAc/Hexane (0-65% gradient) as an eluent. The resulting product was further purified by prep HPLC. The pure fractions were combined and were dried on a lyophilizer. The desired product was obtained as a tan solid (**P-0016**, 6.5 mg, 7.6% yield). MS (ESI) $[M+H^+]^+ = 494.4$. H^1 NMR(THF-d_8) spectrum is consistent with the structure of the compound.

Example 5: Synthesis of N-(2-Chloro-5-{3-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-pyridin-3-yl)-benzenesulfonamide 25

[0221] N-(2-Chloro-5-{3-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-pyridin-3-yl)-benzenesulfonamide **7** was prepared in six steps from 5-Bromo-1H-pyrrolo[2,3-b]pyridine **1** as shown in Scheme 1.

Scheme 5



Step 1 – Preparation of 2,6-Difluoro-3-nitro-phenyl)-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (21):

[0222] To 5-Bromo-1H-pyrrolo[2,3-b]pyridine (**20**, 0.5 g, 2 mmol) in nitromethane (11 mL) was added aluminum trichloride (1.64 g, 12 mmol). The mixture became clear instantly. The resulting solution was stirred at room temperature for 1 hour. To this mixture was then added 2,6-difluoro-3-nitro-benzoyl chloride (0.681 g, 3 mmol) in nitromethane. The reaction mixture was stirred at 45 °C overnight. The reaction was quenched with methanol. After a few minutes, some solids were crashed out. Solids were collected by filtration, and it was clean product (**21,** 0.58 g). Additional product was obtained from filtrate through chromatography (eluted with ethyl acetate and dichloromethane).

[0223] Preparation of 2,6-Difluoro-3-nitro-benzoyl chloride: To 2,6-Difluoro-3-nitro-benzoic acid (2 g, 1 mmol) was added thionyl chloride (0.9 mL, 12 mmol). The reaction mixture was stirred at 57 °C overnight. After removal of solvent, the residue was stripped once from toluene. This gave brown oil was checked by NMR which indicated complete conversion to the acid chloride (18 g, 99%). This material was used as is, without purification.

Step 2 – Preparation of (3-Amino-2,6-difluoro-phenyl)-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (22):

[0224] To a suspension of 2,6-difluoro-3-nitro-phenyl)-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (0.123 g, 0.287 mmol) in ethyl acetate (5 mL) and tetrahydrofuran (5 mL) was added stannous chloride, dihydrate (0.223 g, 1 mmol). The reaction mixture was stirred at 60 °C for 24 hours. The reaction mixture was poured into a mixture of 25 mL of water and 25 mL of saturated sodium bicarbonate. This milky mixture was filtered through a bed of Celite, and the Celite bed was washed with some ethyl acetate. The two layers of the filtrate were separated. The organic layer were collected, washed with brine, and dried over anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by chromatography (eluted with ethyl acetate and dichloromethane) to provide solid product (**22,** 0.1 g, 87%).

Step 3 – Preparation of isobutane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (23):

[0225] A mixture of (3-Amino-2,6-difluoro-phenyl)-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (47 mg, 0.13 mmol), isobutane-1-sulfonylchloride (62 mg, 0.4 mmol), and pyridine (0.5 mL, 6 mmol), in tetrahydrofuran (3 mL) was irradiated in microwave at 130°C for 10 minutes. The mixture was diluted by ethyl acetate and then washed with water, brine, and dried over anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by chromatography (eluted with hexanes and ethyl acetate) to provide desired product (**23**, 24 mg, 36%).

Step 4 – Preparation of isobutane-1-sulfonic acid {2,4-difluoro-3-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (24):

[0226] To a suspension of compound **23**, an appropriate amount of bis(pinacolato)diboron, and potassium acetate in anhydrous 1,4-dioxane or an appropriate solvent is added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II) (complex with dichloromethane 1:1). The suspension is heated in an oil bath for 2 to 24 hours. After cooling to room temperature, the mixture is diluted with ethyl acetate, filtered through a Celite pad, and concentrated. The residue is purification by chromatography to provide isobutane-1-sulfonic acid {2,4-difluoro-3-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (**24**).

Step 5 – Preparation of isobutane-1-sulfonic acid {3-[5-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide (25):

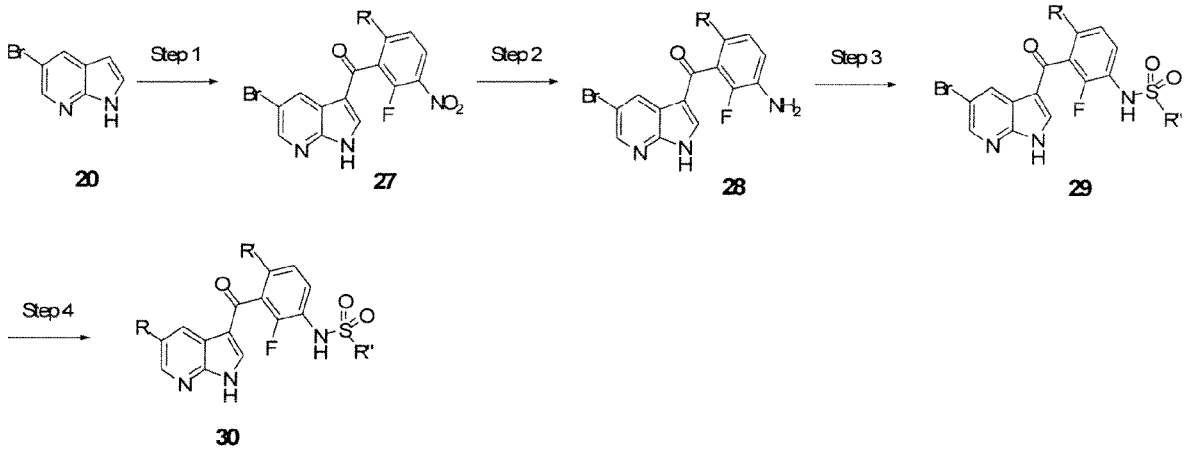
[0227] To a mixture of compound **24**, phenyl bromide and an appropriate amount of cesium carbonate in anhydrous 1,4-dioxane or an appropriate solvent is added an appropriate amount of tetrakis(triphenylphosphine)palladium. The mixture is then heated in an oil bath for 2 to 48 hours. After cooling to room temperature, the mixture is diluted with ethyl acetate or an appropriate solvent, filtered through Celite, and concentrated. The residue is purified by chromatography to provide

isobutane-1-sulfonic acid {3-[5-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide (**25**).

Example 6: Preparation of compound 30

[0228] Compound **30** is prepared in four steps from 5-Bromo-1H-pyrrolo[2,3-b]pyridine **1** as shown in Scheme 2.

Scheme 6



Step 1 – Preparation of compound 27:

[0229] To 5-Bromo-1H-pyrrolo[2,3-b]pyridine (**20**) in nitromethane or an appropriate solvent is added an appropriate amount of aluminum trichloride. The resulting solution is stirred at room temperature for 1 to 24 hour (heated in an oil bath if necessary). To this mixture is then added appropriate amount of benzoyl chloride in nitromethane or an appropriate solvent. The reaction mixture is heated in an oil bath for 2 to 48 hours. The reaction is quenched with methanol or an appropriate solvent. Precipitate is collected by filtration, and it is purified by chromatography to provide compound **27**.

Step 2 – Preparation of compound 28:

[0230] To a suspension of compound **20** in an appropriate solvent is added an appropriate amount of stannous chloride. The reaction mixture is heated in an oil bath for 2 to 48 hours. The reaction mixture is poured into a mixture of water and saturated sodium bicarbonate. This milky mixture was filtered through a bed of Celite, and the Celite bed was washed with an appropriate solvent. The organic layers were collected, washed with brine, and dried over anhydrous sodium sulfate. After removal of drying agent and solvent, the residue is purified by chromatography to provide compound **28**.

Step 3 – Preparation of compound 29:

[0231] A mixture of compound **28**, an appropriate sulfonyl chloride, and an appropriate amount of pyridine in an appropriate solvent is irradiated in microwave at over 50°C for 10 to 60 minutes. The

mixture is diluted by an appropriate solvent and then washed with water, brine, and dried over anhydrous sodium sulfate. After removal of drying agent and solvent, the residue is purified by chromatography to provide compound **29**.

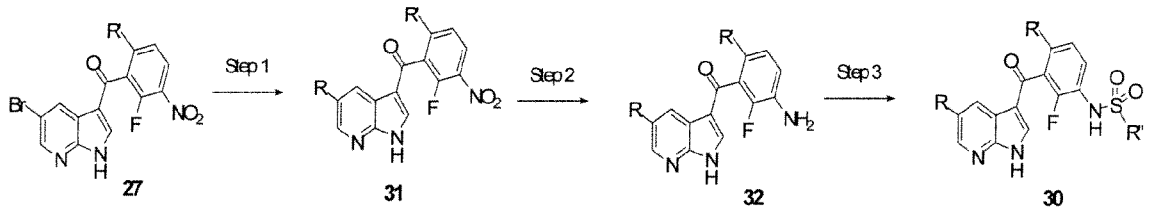
Step 4 – Preparation of compound 30:

[0232] To a mixture of compound **29** , an appropriate boronic acid or a boronic ester, and an appropriate amount of cesium carbonate in anhydrous 1,4-dioxane or an appropriate solvent is added an appropriate amount of tetrakis(triphenylphosphine)palladium. The mixture is then heated in an oil bath for 2 to 48 hours. After cooling to room temperature, the mixture is diluted with ethyl acetate or an appropriate solvent, filtered through Celite, and concentrated. The residue is purification by chromatography to provide compound **30**. When boronic acid or a boronic ester is not commercially available, boronic acid or ester of compound **29** is prepared by following the procedure described at Example 1, step 4. Compound **30** is then prepared by following the abovementioned procedure from boronic acid or ester of compound **29** and an appropriate halide.

Example 7: Preparation of compound 30

[0233] Compound **30** can also be prepared in three steps from 5-Bromo-1H-pyrrolo[2,3-b]pyridine **11** as shown in Scheme 3.

Scheme 7



Step 1 – Preparation of compound 31:

[0234] To a mixture of compound **27** , an appropriate boronic acid or a boronic ester, and an appropriate amount of cesium carbonate in anhydrous 1,4-dioxane or an appropriate solvent is added an appropriate amount of tetrakis(triphenylphosphine)palladium. The mixture is then heated in an oil bath for 2 to 48 hours. After cooling to room temperature, the mixture is diluted with ethyl acetate or an appropriate solvent, filtered through Celite, and concentrated. The residue is purification by chromatography to provide compound **31**. When boronic acid or a boronic ester is not commercially available, boronic acid or ester of compound **27** is prepared by following the procedure described at Example 1, step 4. Compound **31** is then prepared by following the abovementioned procedure from boronic acid or ester of compound **27** and an appropriate halide.

Step 2 – Preparation of compound 32:

[0235] To a suspension of compound **31** in an appropriate solvent is added an appropriate amount of stannous chloride. The reaction mixture is heated in an oil bath for 2 to 48 hours. The reaction mixture is poured into a mixture of water and saturated sodium bicarbonate. This milky mixture was filtered through a bed of celite, and the celite bed was washed with an appropriate solvent. The organic layers were collected, washed with brine, and dried over anhydrous sodium sulfate. After removal of drying agent and solvent, the residue is purified by chromatography to provide compound **32**.

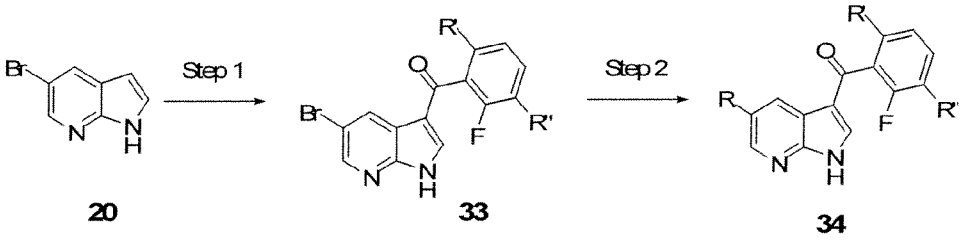
Step 3 – Preparation of compound 30:

[0236] A mixture of compound **32**, an appropriate sulfonyl chloride, and an appropriate amount of pyridine in an appropriate solvent is irradiated in microwave at over 50°C for 10 to 60 minutes. The mixture is diluted by an appropriate solvent and then washed with water, brine, and dried over anhydrous sodium sulfate. After removal of drying agent and solvent, the residue is purified by chromatography to provide compound **30**.

Example 8: Preparation of compound 34

[0237] Compound **34** is prepared in two steps from 5-Bromo-1H-pyrrolo[2,3-b]pyridine **1** as shown in Scheme 8.

Scheme 8.



20 33 34

Step 1 – Preparation of compound 33:

[0238] To 5-Bromo-1H-pyrrolo[2,3-b]pyridine (**20**) in nitromethane or an appropriate solvent is added appropriate amount of aluminum trichloride. The resulting solution is stirred at room temperature for 1 to 48 hour (heated in an oil bath if necessary). To this mixture is then added appropriate amount of benzoyl chloride in nitromethane or an appropriate solvent. The reaction mixture is heated in an oil bath for 2 to 48 hours. The reaction is quenched with an appropriate solvent. Precipitate is collected by filtration, and it is purified by chromatography to provide compound **33**.

Step 2 – Preparation of compound 34:

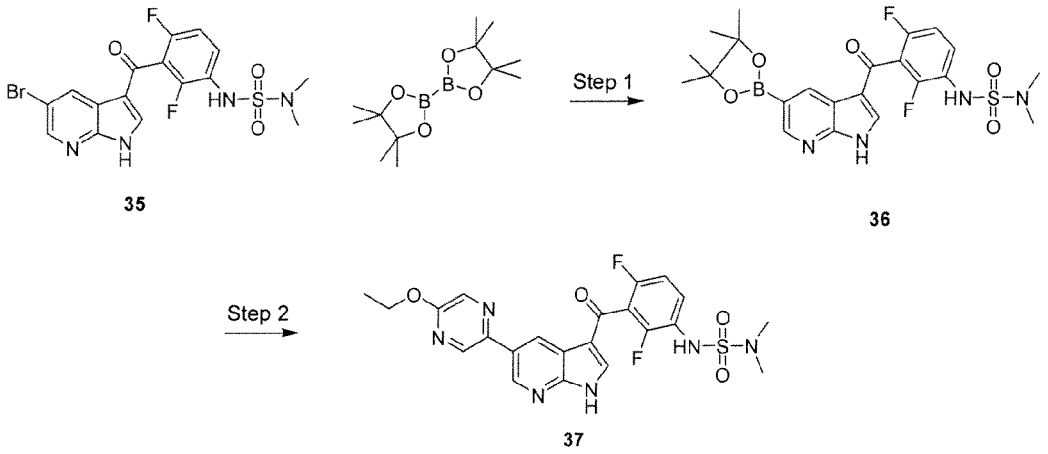
[0239] To a mixture of compound **33** , an appropriate boronic acid or a boronic ester, and an appropriate amount of cesium carbonate in anhydrous 1,4-dioxane or an appropriate solvent is added an appropriate amount of tetrakis(triphenylphosphine)palladium. The mixture is then heated in an oil

bath for 2 to 48 hours. After cooling to room temperature, the mixture is diluted with ethyl acetate or an appropriate solvent, filtered through Celite, and concentrated. The residue is purification by chromatography to provide compound **34**.

[0240] When boronic acid or a boronic ester is not commercially available, boronic acid or ester of compound **33** is prepared by following the procedure described at Example 6, step 4. Compound **34** is then prepared by following the abovementioned procedure from boronic acid or ester of compound **33** and an appropriate halide.

Example 9: Prepartion of 3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-5-(5-ethoxypyrazin-2-yl)-1H-pyrrolo[2,3-b]pyridine (37).

Scheme 9.



Step 1.

[0241] Into a microwave vial 5-bromo-3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridine **35** (70% pure, 200 mg, 0.3 mmol) was placed with 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (216.75 mg, 0.85 mmol) and potassium acetate (100 mg, 1.02 mmol) was added followed by 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (50 mg, 0.06 mmol). 1,4-dioxane (3 mL) was added and the mixture was irradiated in microwave reactor at 145 °C for 45 minutes. The formation of the intermediate **36** was confirmed by LCMS. MS ESI [M+H+]+ = 506.95 [M-H+]- = 504.85.

Step 2.

[0242] 2-Bromo-5-ethoxypyrazine (200 mg, 0.99 mmol) in 1.5 mL of 1,4-dioxane was added into the reaction mixture, made in step 1, followed by the addition of 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (50 mg, 0.06 mmol) and 1M potassium carbonate in water (1.3 ml). The reaction was irradiated in microwave reactor at 135°C for 10 minutes. After cooling the reaction was placed into brine and 1N HCl; the

aqueous were extracted with ethyl acetate. The organic layers were combined and dried over anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by silica gel chromatography eluting with a gradient of ethyl acetate: hexanes (10-100%) to provide 3-[3-(dimethylsulfamoylamino)-2,6-difluoro-benzoyl]-5-(5-ethoxypyrazin-2-yl)-1H-pyrrolo[2,3-b]pyridine **37** (16 mg, 10.2%). ESI [M+H+]+ = 503.0 [M-H+]- = 501.1.

Example 10: Compound Properties

[0243] While the inhibitory activity of the compounds on any Raf kinase is important to their activity in treating of disease, the compounds described herein show favorable properties that provide advantages as a pharmaceutical as well.

[0244] Assays for biochemical and cell based activity are known in the art, for example, as described in PCT publication WO 2007/002433, the disclosure of which is hereby incorporated by reference as it relates to such assays. For example, the biochemical activity IC_{50} values are determined with respect to inhibition of B-Raf V600E kinase activity or p-Erk kinase activity, where inhibition of phosphorylation of a peptide substrate is measured as a function of compound concentration. Compounds to be tested are diluted in dimethyl sulfoxide to a concentration of 0.1 mM. These are serially diluted 15 µL into 30 µL of dimethyl sulfoxide seven times in 96 well plates for a total of 8 dilution points, and for each dilution point 1 µL is added to a well of an assay plate. Plates are prepared such that each well in a 384 well plate contains 1 µL of compound in 10 µL volume with 0.1 ng Raf enzyme (i.e. any of B-Raf, c-Raf-1 or B-Raf V600E, Upstate Biotechnology or preparead by methods known to one of skill in the art), 50 mM HEPES, pH 7.0, 50 mM NaCl, 2 mM $MgCl_2$, 1 mM $MnCl_2$, 0.01% Tween-20, 1 mM DTT, and 100 nM biotin-MEK1 as substrate. The reaction is started with addition of 10 µL of 200 µM ATP (i.e. final 100 µM ATP). After incubation of the kinase reaction for 45 minutes at room temperature, 5 µL/well of Stop Solution is added (25 mM Hepes pH 7.5, 100 mM EDTA, 0.01% BSA with donor beads (Streptavidin coated beads, Perkin Elmer), acceptor beads (Protein A coated, Perkin Elmer), and anti phosphor MEK1/2 antibody (CellSignal), each at final concentration 10 µg/mL). The plates are incubated for 3 hours at room temperature and read on Envision reader (Perkin Elmer). Phosphorylation of Mek1 results in binding of the anti-phosphor-MEK1/2antibody and association of the donor and acceptor beads such that signal correlates with kinase activity. The signal vs. compound concentration is used to determine the IC_{50}.

[0245] Compounds are assessed in a variety of cell based assays. For example human cell lines with B-Raf V600E mutation (A375 melanoma, SKMEL3 melanoma, and COLO205 colon adenocarcinoma), as well as tumorigenic cell lines with wild-type B-RAF (SW620 colon adenocarcinoma) or with Ras mutations (SKMEL2 melanoma and IPC298 melanoma). Similar assays may be used to assess additional tumorigenic cell lines with Ras mutations, including, but not limited to, M202, M207, M243, M244, M296, S117, HCT116, HCT15, DLD1, MiaPaCa, A549, NCI-

H23, NCI-H460, HOP62, MDA-MB231, Hs-578T, HL60, MOLT-4, and CCRF-CEM.

[0246] On day 1, cells are counted, then centrifuged in a conical tube for 5 minutes at 1000 rpm. The supernatant is removed and cells are re-suspended as follows:

SW620 (ATCC catalog # CCL-27): resuspend in Leibovitz's L-15 medium, 2 mM L-glutamine, 10% fetal bovine serum to 6 X 10^4 cells/mL.

A375 (ATCC catalog # CRL-1619): resuspend in Dulbecco's modified Eagle's medium, 4 mM L-glutamine, 4.5 g/L D-glucose, 10% fetal bovine serum to 6 X 10^4 cells/mL.

COLO205 (ATCC catalog # CCL-222): resuspend in RPMI 1640, 2 mM L-glutamine, 1.5 g/L sodium bicarbonate, 4.5 g/L D-glucose, 10 mM HEPES, 1.0 mM sodium pyruvate, 10% fetal bovine serum to 6 X 10^4 cells/mL.

SKMEL2 (ATCC catalog # HTB-68): resuspend in Minimum Eagle essential medium, 2 mM L-glutamine, 1.5 g/L sodium bicarbonate, 0.1 mM non-essential amino acids, 1.0 mM sodium pyruvate, 10% fetal bovine serum to 6 X 10^4 cells/mL.

SKMEL3 (ATCC catalog # HTB-69): resuspend in McCoy's 5A medium, 1.5 mM L-glutamine, 15% fetal bovine serum to 6 X 10^4 cells/mL.

IPC298 (DSMZ catalog # ACC 251): resuspend in RPMI 1640, 2 mM L-glutamine, 10% fetal bovine serum to 6 X 10^4 cells/mL.

[0247] The cells are plated, 50 µL in each well of a 96-well dish (Corning 3610) and incubated at 37 °C in 5% CO_2 overnight, cells plated to a final concentration of cells as follows:

SW620: 5,000 cells per well.

A375: 2,000 cells per well.

COLO205: 2,000 cells per well.

SKMEL2: 2,000 cells per well.

SKMEL3: 3,000 cells per well.

IPC298: 2,000 cells per well.

[0248] On day 2, compound at a maximum concentration of 5 mM is serially diluted 1:3 (e.g. 10 µL with 30 µL dimethyl sulfoxide) for a total of 8 point titration with DMSO as a control. A 1 µL aliquot of each dilution point and control is added to 249 µL growth media and 50 µL is added to a well containing cells, providing 10 µM compound at the maximum concentration point. The cells are incubated for 3 days at 37 °C in 5% CO_2.

[0249] On day 5, ATPlite 1 step Luminescence Assay System (Perkin Elmer # 6016739) is brought to room temperature along with the cell cultures. ATPlite is added 25 µL to each well, shake for 2 minutes, and the cells are incubated at room temperature for 10 minutes, then luminescence is read on

Safire reader. The measured luminescence correlates directly with cell number, such that the reading as a function of compound concentration is used to determine the IC_{50} value.

[0250] B9 is a squamous cell carcinoma cell line expressing activated HRAS that was isolated from a DMBA/TPA-induced mouse model of skin carcinogenesis (Stoler, et al. *The Journal of Cell Biology*, 1993, *122*(5), 1103-17). IPC-298 is a human melanoma cell line that expresses activated NRAS (Aubert, et al. *International Journal of Cancer*, 1993, *54*(5), 784-92). To determine whether compounds induce phosphorylated ERK and MEK, cells are plated in a 96-well dish and treated with an 8-point titration of compound for one hour at 37 °C. The media is then removed and the cells are incubated with lysis buffer containing protease and phosphatase inhibitors. Phosphorylated ERK and MEK in the resulting lysates is detected using AlphaScreen™ technology. To detect phosphorylated ERK, cell lysates are incubated with streptavidin-coated donor beads, anti-mouse IgG acceptor beads, a biotinylated anti-ERK1/2 rabbit antibody, and a mouse antibody that recognizes ERK1/2 only when it is phosphorylated on Thr202 and Tyr204. The biotinylated ERK1/2 antibody will bind to both the streptavidin-coated donor beads and to ERK1/2 (regardless of its phosphorylation state), and the phospho-ERK1/2 antibody will bind to the acceptor beads and to ERK1/2 that is phosphorylated at Thr202/Tyr204. Excitation of the beads with laser light at 680 nm produces singlet oxygen, which is rapidly quenched unless the beads are in close proximity. When ERK is phosphorylated, both antibodies can bind the same protein, bringing the donor and acceptor beads into close proximity, producing a signal that can be measured at 580 nm. MEK phosphorylation is detected using a similar approach, only with antibodies directed against total MEK1/2 and MEK1/2 that is phosphorylated at Ser217 and Ser221.

[0251] It is understood that the results of these assays may vary as assay conditions are varied. Inhibition levels determined under the conditions described herein represent a relative activity for the compounds tested under the specific conditions employed. The cell based assays are likely to show variability due to the complexity of the system and the sensitivity thereof to any changes in the assay conditions. As such, some level of inhibition in the cell based assays is indicative of the compounds having some inhibitory activity for those cells, whereas lack of inhibition below the threshold of the highest concentration tested does not necessarily indicate that the compound has no inhibitory activity on the cells, only that under the conditions tested, no inhibition is observed. In some instances, the compounds were not tested in all of the assays, or assay results were not valid, as indicated by NA in the tables below.

[0252] The following table provides data indicating the B-Raf V600E and IPC-298_P-ERK cell activation activity, A375_P-ERK and COLO205 cell growth inhibitory activity for exemplary compounds as described herein:

Compound number	Biochemical activity (IC_{50} μM)	Cell activity (EC_{50} μM)	Cell activity (IC_{50} μM)	
	V600E	IPC-298_P-ERK	A375	COLO205
P-0012	< 0.1	> 10	< 1	> 1

Compound number	Biochemical activity (IC_{50} μM)	Cell activity (EC_{50} μM)	Cell activity (IC_{50} μM)	
	V600E	IPC-298 P-ERK	A375	COLO205
P-0013	< 0.1	> 10	< 1	> 1
P-0014	< 0.1	> 8	< 1	< 1
P-0015	< 0.1	> 10	< 1	> 1
P-0016	< 0.1	NA	< 1	< 1
P-0017	< 0.1	> 10	< 1	> 1
P-0018	< 0.1	> 10	< 1	> 1
P-0019	< 0.1	> 10	< 1	> 1
P-0020	< 0.1	> 10	< 1	< 1
P-0021	< 0.1	> 10	< 1	< 1
P-0022	< 0.1	> 10	< 1	< 1
P-0023	< 0.1	> 10	< 1	> 1
P-0024	< 0.1	> 10	< 1	> 1
P-0025	< 0.1	> 10	< 1	< 1
P-0026	> 0.1	> 10	> 1	
P-0027	< 0.1	NA	< 1	< 1
P-0028	< 0.1	> 10	< 1	< 1
P-0029	< 0.1	> 10	< 1	< 1
P-0030	< 0.1	> 10	< 1	< 1
P-0031	< 0.1	> 10	< 1	< 1
P-0032	< 0.1	> 10	< 1	< 1
P-0033	< 0.1	> 10	< 1	< 1
P-0034	< 0.1	> 10	< 1	> 1
P-0035	< 0.1	> 10	< 1	> 1
P-0036	< 0.1	> 10	< 1	> 1
P-0037	< 0.1	> 10	< 1	> 1
P-0038	< 0.1	> 10	< 1	> 1
P-0039	< 0.1	> 10	< 1	> 1
P-0040	< 0.1	> 10	< 1	< 1
P-0041	> 0.1	> 10	> 1	
P-0042	< 0.1	> 10	< 1	< 1
P-0043	< 0.1	> 10	< 1	< 1
P-0044	< 0.1	> 10	< 1	< 1
P-0045	< 0.1	> 10	< 1	< 1
P-0046	< 0.1	> 10	< 1	< 1
P-0047	< 0.1	> 10	< 1	< 1
P-0048	< 0.1	> 10		< 1
P-0049	< 0.1	> 4	< 1	< 1
P-0050	< 0.1	> 10	< 1	< 1
P-0051	< 0.1	> 10	< 1	< 1
P-0052	< 0.1	> 10	< 1	< 1
P-0053	< 0.1	> 10	< 1	< 1
P-0054	< 0.1	> 1	< 1	> 1
P-0055	< 0.1	> 10	< 1	< 1
P-0056	< 0.1	> 10	< 1	< 1
P-0057	< 0.1	> 10	< 1	< 1
P-0058	< 0.1	> 10	< 1	< 1
P-0059	< 0.1	> 10	< 1	< 1
P-0060	< 0.1	> 2	< 1	< 1
P-0061	< 0.1	> 10	< 1	< 1
P-0062	< 0.1	> 10	< 1	< 1
P-0063	< 0.1	> 10	< 1	< 1
P-0064	< 0.1	> 10	< 1	< 1

Compound number	Biochemical activity (IC_{50} μM)	Cell activity (EC_{50} μM)	Cell activity (IC_{50} μM)	
	V600E	IPC-298_P-ERK	A375	COLO205
P-0065	< 0.1		< 1	> 1
P-0066	< 0.1		< 1	< 1
P-0067	< 0.1		< 1	> 1
P-0068	< 0.1			
P-0069	< 0.1			
P-0070	> 0.1		< 1	> 1
P-0071	> 0.1		< 1	> 1
P-0072	> 0.1		< 1	> 1
P-0073	> 0.1		< 1	> 1
P-0074	> 0.1		< 1	> 1
P-0075	> 0.1		< 1	> 1
P-0076	< 0.1		< 1	< 1
P-0077	< 0.1		< 1	< 1
P-0078	< 0.1		< 1	> 1
P-0079	< 0.1		< 1	< 1
P-0080	< 0.1		< 1	> 1
P-0081	< 0.1		< 1	< 1
P-0082	< 0.1		< 1	< 1
P-0083	< 0.1		< 1	< 1
P-0084	< 0.1		< 1	< 1
P-0085	< 0.1		< 1	> 1
P-0086	< 0.1		< 1	< 1
P-0087	< 0.1		< 1	< 1
P-0088	< 0.1		< 1	> 1
P-0089	< 0.1		< 1	> 1
P-0090	< 0.1		< 1	< 1
P-0091	< 0.1		< 1	< 1
P-0092	< 0.1		< 1	< 1
P-0093	< 0.1		< 1	< 1
P-0094	< 0.1		< 1	< 1
P-0095	< 0.1		< 1	< 1
P-0096	< 0.1		< 1	< 1
P-0097	< 0.1		< 1	< 1
P-0098	< 0.1		< 1	< 1
P-0099	< 0.1		< 1	> 1
P-0100	< 0.1		< 1	> 1
P-0101	< 0.1		< 1	> 1
P-0102	< 0.1		< 1	> 1
P-0103	< 0.1		< 1	< 1
P-0104	< 0.1		< 1	< 1
P-0105	< 0.1		< 1	< 1
P-0106	< 0.1		< 1	< 1
P-0107	< 0.1		< 1	< 1
P-0108	< 0.1		< 1	> 1
P-0109	< 0.1		< 1	< 1
P-0235	< 0.1		< 1	< 1
P-0236	< 0.1		< 1	< 1
P-0237	< 0.1		< 1	< 1
P-0238	< 0.1		< 1	< 1
P-0239	< 0.1		< 1	< 1
P-0240	< 0.1		< 1	< 1
P-0241	< 0.1		< 1	< 1

Compound number	Biochemical activity (IC_{50} μM)	Cell activity (EC_{50} μM)	Cell activity (IC_{50} μM)	
	V600E	IPC-298_P-ERK	A375	COLO205
P-0242	< 0.1		> 1	> 1
P-0243	< 0.1		> 1	> 1
P-0244	< 0.1		> 1	> 1
P-0245	< 0.1		< 1	< 1
P-0246	< 0.1		> 1	> 1
P-0247	< 0.1		< 1	< 1
P-0248	< 0.1		< 1	< 1
P-0249	< 0.1		< 1	< 1
P-0251	< 0.1		> 1	> 1
P-0252	< 0.1		< 1	< 1
P-0253	< 0.1		> 1	> 1
P-0254	< 0.1		< 1	< 1
P-0255	< 0.1		< 1	< 1
P-0256	< 0.1		< 1	< 1
P-0257	> 0.1			> 1
P-0258	< 0.1		< 1	< 1
P-0259	< 0.1		< 1	< 1
P-0260	< 0.1		< 1	< 1
P-0261	< 0.1		< 1	< 1
P-0262	< 0.1		< 1	< 1
P-0263	< 0.1		< 1	< 1
P-0264	< 0.1		< 1	< 1
P-0265	< 0.1	> 2	< 1	< 1
P-0266	< 0.1		< 1	< 1
P-0267	> 0.1			
P-0268	< 0.1		< 1	< 1
P-0269	< 0.1		< 1	< 1
P-0270	< 0.1		< 1	< 1
P-0271	< 0.1		< 1	< 1
P-0272	> 0.1			
P-0273			< 1	< 1
P-0274	< 0.1		< 1	> 1
P-0275	< 0.1		< 1	< 1
P-0276	< 0.1		< 1	> 1
P-0277	> 0.1		< 1	< 1
P-0279	< 0.1		> 1	< 1
P-0280			< 1	< 1
P-0281	< 0.1		< 1	< 1
P-0282	< 0.1		< 1	< 1
P-0283	< 0.1		> 1	< 1
P-0284			< 1	< 1
P-0285	< 0.1		< 1	< 1
P-0286	< 0.1		> 1	< 1
P-0287		> 4	< 1	< 1
P-0288	< 0.1	> 2	< 1	< 1
P-0289	< 0.1		< 1	< 1
P-0291	> 0.1			
P-0292			< 1	< 1
P-0293	< 0.1		< 1	< 1
P-0294	< 0.1		> 1	> 1
P-0295	< 0.1	> 2	< 1	< 1

Compound number	Biochemical activity (IC_{50} μM)	Cell activity (EC_{50} μM)	Cell activity (IC_{50} μM)	
	V600E	IPC-298_P-ERK	A375	COLO205
P-0297	< 0.1		> 1	> 1
P-0298	< 0.1		> 1	> 1
P-0299	< 0.1		> 1	> 1
P-0300	< 0.1	> 4	< 1	> 1
P-0301	< 0.1		< 1	> 1
P-0302	< 0.1		< 1	< 1
P-0303	< 0.1		> 1	> 1
P-0304	< 0.1		< 1	< 1
P-0305	< 0.1		< 1	< 1
P-0306	< 0.1		> 1	< 1
P-0307	< 0.1		< 1	< 1
P-0308	< 0.1		< 1	< 1
P-0309	< 0.1		< 1	< 1
P-0310	< 0.1		< 1	< 1
P-0311	< 0.1		< 1	< 1
P-0312	< 0.1		< 1	< 1
P-0313	< 0.1		< 1	< 1
P-0314	< 0.1		< 1	< 1
P-0315	< 0.1		< 1	< 1
P-0316	< 0.1		< 1	< 1
P-0317	< 0.1		< 1	< 1
P-0318	< 0.1		< 1	< 1
P-0319	< 0.1		< 1	< 1
P-0320	> 0.1			
P-0321	< 0.1		< 1	< 1
P-0322	< 0.1		< 1	< 1
P-0324	< 0.1		< 1	< 1
P-0325	< 0.1		< 1	> 1
P-0326	< 0.1		> 1	> 1
P-0327	< 0.1		< 1	< 1
P-0334	< 0.1	> 2	> 1	> 1
P-0335	< 0.1		< 1	< 1
P-0336	> 0.1	> 4		
P-0337	< 0.1		> 1	> 1
P-0338	< 0.1		< 1	< 1
P-0339	< 0.1		< 1	< 1
P-0340	< 0.1		< 1	< 1
P-0223	> 0.1			
P-0224	< 0.1		< 1	< 1
P-0225	< 0.1		< 1	< 1
P-0226	< 0.1		< 1	< 1
P-0227	< 0.1		< 1	< 1
P-0228	< 0.1		< 1	< 1
P-0229	< 0.1		< 1	< 1
P-0230	< 0.1		< 1	< 1
P-0231	< 0.1		< 1	< 1
P-0232	< 0.1		< 1	< 1
P-0233	< 0.1		> 1	> 1
P-0117	> 0.1		> 1	> 1
P-0116	< 0.1		< 1	< 1
P-0115	< 0.1		< 1	< 1
P-0114	< 0.1		< 1	< 1

Compound number	Biochemical activity (IC_{50} μM)	Cell activity (EC_{50} μM)	Cell activity (IC_{50} μM)	
	V600E	IPC-298_P-ERK	A375	COLO205
P-0113	< 0.1		< 1	< 1
P-0112	< 0.1		< 1	< 1
P-0111	< 0.1		< 1	< 1
P-0110	< 0.1		< 1	< 1

[0253] The table below provides the IPC-298_P-ERK cell activation activity, A375_P-ERK and COLO205 cell growth inhibitory activity data for a few exemplary compounds known in the art.

Compound	Cell activity (EC_{50} μM)	Cell activity (IC_{50} μM)	
	IPC-298_P-ERK	A375	COLO205
N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]propane-1-sulfonamide	< 0.5	< 0.8	< 1
N-[2,4-difluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]-2-fluoro-benzenesulfonamide	< 0.5	< 0.5	< 1
N-[2,4-difluoro-3-[5-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]phenyl]-2,5-difluoro-benzenesulfonamide	< 1	< 0.5	< 1

[0254] Pharmacokinetic properties of compounds (including any solid forms or formulations thereof) are assessed in male Sprague Dawley rats or male Beagle dogs. Rats are dosed daily with compound either by IV injections via surgically implanted jugular catheters or by oral gavage (PO). Each compound is prepared as a 20 mg/mL stock solution in dimethyl sulfoxide, which is further diluted to provide the dosing stock at the desired concentration for the IV or PO formulations. For IV dosing, the dosing stock is diluted into a 1:1:8 mixture of Solutol ®:ethanol:water. For PO dosing, the dosing stock is diluted into 1% methylcellulose. In a cassette format (or each compound, solid form thereof or formulation thereof is done individually), compounds are diluted to 0.5 mg/mL each for IV dosing and 0.4 mg/mL each for PO dosing and dosed at 1 mg/kg (2mL/kg) or 2 mg/kg (5 mL/kg), respectively. For IV dosed animals, tail vein blood samples are collected with lithium heparin anticoagulant at 5, 15, 30, and 60 minutes and 4, 8, and 24 hours post dosing each day. For PO dosed animals, tail vein blood samples are collected with lithium heparin anticoagulant at 30 minutes, 1, 2, 4, 8 and 24 hours post dosing each day. Dogs are dosed daily by oral capsules in a suitable formulation at 50 mg/mL. Cephalic vein blood samples are collected with lithium heparin anticoagulant at 30 minutes, 1, 2, 4, 8 and 24 hours post dosing each day. All samples are processed to plasma and frozen for later analysis of each compound by LC/MS/MS. Plasma levels as a function of time are plotted to assess the AUC (ng*hr/mL). Compounds according to the present invention preferably show improved pharmacokinetic properties relative to previously described compounds, i.e. they have substantially higher values for one or more of AUC, Cmax and half-life relative to previously described compounds.

[0255] All patents, patent applications and other references cited in the specification are indicative

of the level of skill of those skilled in the art to which the invention pertains, and are incorporated by reference in their entireties, including any tables and figures, to the same extent as if each reference had been incorporated by reference in its entirety individually.

[0256] One skilled in the art would readily appreciate that the present invention is well adapted to obtain the ends and advantages mentioned, as well as those inherent therein. The methods, variances, and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

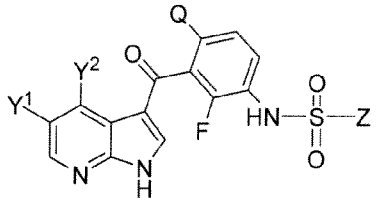
[0257] While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention.

[0258] In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

[0259] Also, unless indicated to the contrary, where various numerical values are provided for embodiments, additional embodiments are described by taking any two different values as the endpoints of a range. Such ranges are also within the scope of the described invention.

WHAT IS CLAIMED IS:

1. A compound of formula I:



I

or pharmaccutically acceptable salts, hydrates, solvates, tautomers and isomers, thereof;

wherein:

Y^1 is selected from the group consisting of CN, halogen, -OH, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{3-6}cycloalkyl, optionally substituted C_{1-6}haloalkyl, optionally substituted C_{1-6}haloalkoxy, optionally substituted aryl and optionally substituted heteroaryl; optionally wherein the two adjacent substituents on the aryl or heteroaryl ring together with the atoms to which they are attached form an optionally substituted 5- or 6-membered ring having from 0 to 3 additional heteroatoms selected from N, O or S;

Y^2 is H, halogen, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, C_{3-8}cycloalkyl-C_{0-4}alkyl or $(R^2)(R^3)N$-, wherein R^2 and R^3 are each independently selected from the group consisting of H, C_{1-6}alkyl, C_{1-6}alkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, C_{3-8}cycloalkyl-C_{0-4}alkyl, heterocycloalkyl and heterocycloalkyl-C_{1-4}alkyl; or R^2 and R^3 taken together with the nitrogen atom to which they are attached form a three to eight-membered ring having from 0-2 additional heteroatoms as ring members selected from N, O or S; wherein Y^2 is optionally substituted with from one to three groups independently selected from R^e;

Q is selected from H, F, Cl or CH_3;

Z is $-N(R^4)(R^5)$ or $-C(R^6)(R^7)(R^8)$, wherein

R^4 and R^5 are each independently selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted C_{3-8}cycloalkylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl; or

R^4 and R^5 taken together with the nitrogen atom to which they are attached form a four to eight-membered ring having from 0-2 additional heteroatoms as ring members selected from N, O or S, wherein the four to eight-membered ring is optionally substituted;

R^6, R^7 and R^8 are each independently H, optionally substituted C_{1-6}alkyl, optionally substituted, C_{1-6}haloalkyl, optionally substituted C_{1-6}haloalkoxy, optionally substituted C_{3-8}cycloalkyl, optionally substituted C_{3-8}cycloalkylalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl or $-X^2R^9$, wherein X^2 is $-NR^{10}$, O or S; R^{10} is H, C_{1-6}alkyl or aryl; and R^9 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, wherein R^9 is optionally substituted with from 1 to 3 R^e substituents; or any two of the R^6, R^7 and R^8 groups taken together with the carbon atom to which they are attached form a 3 to 8-membered optionally substituted non-aromatic ring having from 0 to 2 heteroatoms selected from N, O or S; provided at each occurrence, at least two of the R^6, R^7 and R^8 groups are not simultaneously hydrogen; and

with the proviso when (i) Y^1 is halogen, $-CH_3$, -CN, -OMe or 2-methoxypyrimidin-5-yl, Z is other than dimethylamino, diethylamino, 1-pyrrolidine, 1-piperidinyl, 4-morpholinyl, isopropyl, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_3)(CH_2CH_2CH_3)$, cyclobutyl, cyclopentyl or cyclohexyl; and (ii) when Y^1 is 1-methyl-4-pyrazolyl, 3-methylsulfonylphenyl or 3-methylsulfonylaminophenyl, Z is other than cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

2. The compound of claim 1, wherein

Y^1 is CN, halogen, -OH, C_{1-6} alkyl, C_{1-6} alkoxy, optionally substituted C_{3-6}cycloalkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, aryl and heteroaryl, wherein the aliphatic or aromatic portion of Y^1 is each independently optionally substituted with from 1-5 R^1 substituents; each R^1 is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-4}-alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl or $-R^a$, wherein R^a is selected from halogen, $-CH=CH_2$, -CN, -OH, $-NH_2$, $-NO_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^b$, $-SR^b$, $-OC(O)R^b$, $-OC(S)R^b$, $-C(O)R^b$, $-C(S)R^b$, $-C(O)OR^b$, $-C(S)OR^b$, $-S(O)R^b$, $-S(O)_2R^b$, $-C(O)NHR^b$, $-C(S)NHR^b$, $-C(O)NR^bR^b$, $-C(S)NR^bR^b$, $-S(O)_2NHR^b$, $-S(O)_2NR^bR^b$, $-C(NH)NHR^b$, $-C(NH)NR^bR^b$, $-NHC(O)R^b$, $-NHC(S)R^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NHS(O)_2R^b$, $-NR^bS(O)_2R^b$, $-NHC(O)NHR^b$, $-NHC(S)NHR^b$, $-NR^bC(O)NH_2$, $-NR^bC(S)NH_2$, $-NR^bC(O)NHR^b$, $-NR^bC(S)NHR^b$, $-NHC(O)NR^bR^b$, $-NHC(S)NR^bR^b$, $-NR^bC(O)NR^bR^b$, $-NR^bC(S)NR^bR^b$, $-NHS(O)_2NHR^b$, $-NR^bS(O)_2NH_2$, $-NR^bS(O)_2NHR^b$, $-NHS(O)_2NR^bR^b$, $-NR^bS(O)_2NR^bR^b$, $-NHR^b$ or $-NR^bR^b$, wherein each R^b is independently selected from the group consisting of C_{1-6}alkyl, halogen, -CN, C_{1-6}alkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-4}-alkyl, -OH, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, aryl, aryl-C_{1-4}alkyl, heteroaryl and heteroarylalkyl; or two R^b substituents when attached to the same nitrogen atom taken together with the nitrogen atom form a three to eight-membered ring having from 0-2 additional heteroatoms as ring members selected from N, O or S; wherein the aliphatic or aromatic portion of R^1 is further optionally substituted with from 1-3 groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl or $-R^c$, wherein each R^c is independently selected from halogen, $-CH=CH_2$, -CN, -OH, $-NH_2$, $-NO_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^d$, $-SR^d$, $-OC(O)R^d$, $-OC(S)R^d$, $-C(O)R^d$, $-C(S)R^d$, $-C(O)OR^d$, $-C(S)OR^d$, $-S(O)R^d$, $-S(O)_2R^d$, $-C(O)NHR^d$, $-C(S)NHR^d$, $-C(O)NR^dR^d$, $-C(S)NR^dR^d$, $-S(O)_2NHR^d$, $-S(O)_2NR^dR^d$, $-C(NH)NHR^d$, $-C(NH)NR^dR^d$, $-NHC(O)R^d$, $-NHC(S)R^d$, $-NR^dC(O)R^d$, $-NR^dC(S)R^d$, $-NHS(O)_2R^d$, $-NR^dS(O)_2R^d$, $-NHC(O)NHR^d$, $-NHC(S)NHR^d$, $-NR^dC(O)NH_2$, $-NR^dC(S)NH_2$, $-NR^dC(O)NHR^d$, $-NR^dC(S)NHR^d$, $-NHC(O)NR^dR^d$, $-NHC(S)NR^dR^d$, $-NR^dC(O)NR^dR^d$, $-NR^dC(S)NR^dR^d$, $-NHS(O)_2NHR^d$, $-NR^dS(O)_2NH_2$, $-NR^dS(O)_2NHR^d$, $-NHS(O)_2NR^dR^d$, $-NR^dS(O)_2NR^dR^d$, $-NHR^d$, R^f or $-NR^dR^d$, wherein each R^d is independently selected from C_{1-6}alkyl, arylalkyl, aryl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl or heterocycloalkylalkyl; and wherein the aromatic portion of R^1 is optionally substituted with from 1-3 substituents independently selected from R^e, wherein R^e is selected from the group consisting of halogen, -CN, $-CH=CH_2$, -OH, $-NH_2$, $-NO_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^f$, $-SR^f$, $-OC(O)R^f$, $-OC(S)R^f$, $-C(O)R^f$, $-C(S)R^f$, $-C(O)OR^f$, $-C(S)OR^f$, $-S(O)R^f$, $-S(O)_2R^f$, $-C(O)NHR^f$, $-C(S)NHR^f$, $-C(O)NR^fR^f$, $-C(S)NR^fR^f$, $-S(O)_2NHR^f$, $-S(O)_2NR^fR^f$, $-C(NH)NHR^f$,

$-C(NH)NR^fR^f$, $-NHC(O)R^f$, $-NHC(S)R^f$, $-NR^fC(O)R^f$, $-NR^fC(S)R^f$, $-NHS(O)_2R^f$, $-NR^fS(O)_2R^f$, $-NHC(O)NHR^f$, $-NHC(S)NHR^f$, $-NR^fC(O)NH_2$, $-NR^fC(S)NH_2$, $-NR^fC(O)NHR^f$, $-NR^fC(S)NHR^f$, $-NHC(O)NR^fR^f$, $-NHC(S)NR^fR^f$, $-NR^fC(O)NR^fR^f$, $-NR^fC(S)NR^fR^f$, $-NHS(O)_2NHR^f$, $-NR^fS(O)_2NH_2$, $-NR^fS(O)_2NHR^f$, $-NHS(O)_2NR^fR^f$, $-NR^fS(O)_2NR^fR^f$, $-NHR^f$, $-NR^fR^f$ and R^f, wherein R^f is C_{1-6}alkyl or aryl; or two adjacent R^1 groups on the aryl or heteroaryl ring together with the atoms to which they are attached form a 5- or 6-membered ring having from 0 to 2 additional heteroatoms selected from N, O or S, optionally substituted with from 1 to 3 R^d substituents;

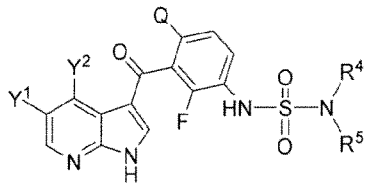
R^4 and R^5 are each independently selected from the group consisting of H, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl, wherein R^4 or R^5 is optionally substituted with from 1 to 3 members independently selected from C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or R^e; or R^4 and R^5 taken together with the nitrogen atom to which they are attached form a four to eight membered ring having from 0-2 additional heteroatoms as ring members selected from N, O or S, wherein said four to eight membered ring is optionally substituted with from one to three groups independently selected from C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl or R^e; and

R^6, R^7 and R^8 are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkylalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl or $-X^2R^9$; wherein the aliphatic or aromatic portion of R^6, R^7 and R^8 are each optionally substituted with from 1 to 3 members independently selected from the group consisting of C_{3-8} cycloalkyl, C_{3-8} cycloalkylalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl and R^e; or any two of the R^6, R^7 and R^8 groups taken together with the carbon atom to which they are attached form a 3 to 8-membered carbocyclic ring or a 4 to 8-membered heterocyclic ring having from 1 to 2 heteroatoms as ring members selected from N, O or S, wherein the 3 to 8-membered carbocyclic ring or the 4 to 8-membered heterocyclic ring is optionally substituted with from one to three groups independently selected from C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}alkyl optionally substituted with R^e, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or R^e.

3. The compound of claim **2**, wherein Y^1 is aryl or heteroaryl groups, wherein the heteroaryl group has from 1 to 4 heteroatoms as ring members selected from N, O or S; and wherein the aryl or heteroaryl groups are optionally substituted with from 1 to 3 R^1 substituents.

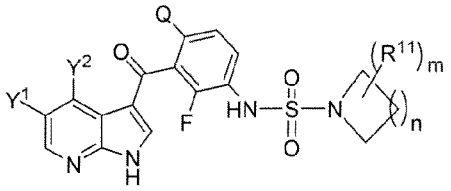
4. The compound of claim **1**, wherein Y^1 is CN, halogen, -OH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6}haloalkyl or C_{1-6}haloalkoxy.

5. The compound of claim **1**, having formula (Ia):



Ia.

6. The compound of claim **1**, having formula (Ib):



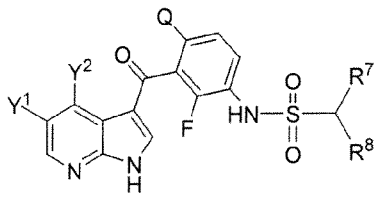
Ib

wherein R^{11} is C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl or R^e;

the subscript m is an integer from 0 to 3; and

the subscript n is an integer from 1 to 5.

7. The compound of claim **1**, having formula (Ic):



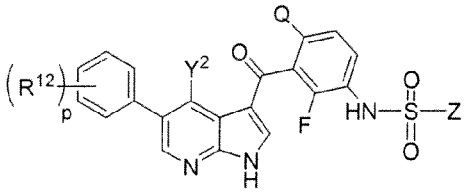
Ic

wherein R^7 and R^8 are each independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or $-X^2R^9$, wherein the aliphatic or aromatic portion of R^7 and R^8 are each optionally substituted with from 1 to 3 members independently selected from the group consisting of C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and R^e, provided at each occurrence, at least two of the R^6, R^7 and R^8 groups are not simultaneously hydrogen; and wherein X^2 is $-NR^{10}$, O or S; R^{10} is H, C_{1-6}alkyl or aryl; and R^9 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, wherein R^9 is optionally substituted with from 1 to 3 R^e substituents; or

R^7 and R^8 groups taken together with the carbon atom to which they are attached form a 3 to 8-membered carbocyclic ring or a 4 to 8-membered heterocyclic ring having from 1 to 2 heteroatoms as ring members selected from N, O or S, wherein the 3 to 8-membered carbocyclic ring or the 4 to 8-

membered heterocyclic ring is optionally substituted with from one to three groups independently selected from C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or R^e.

8. The compound of claim **1**, having formula (Id):



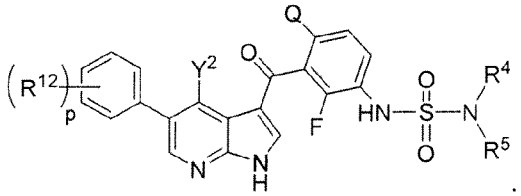
Id

wherein:

R^{12} is H or R^1; or two adjacent R^{12} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; and

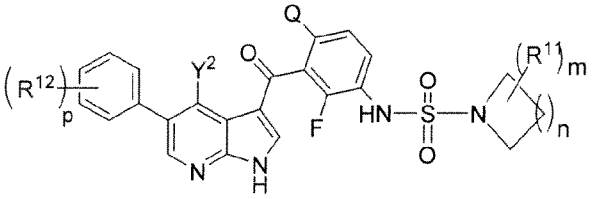
the subscript p is an integer of 1 to 5.

9. The compound of claim **8**, having formula (Id-1):



. Id-1

10. The compound of claim **8**, having formula (Id-2):



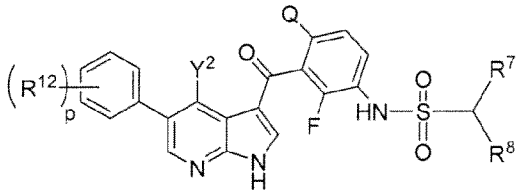
Id-2

wherein R^{11} is C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl or R^e;

the subscript m is an integer from 0 to 3; and

the subscript n is an integer from 1 to 5.

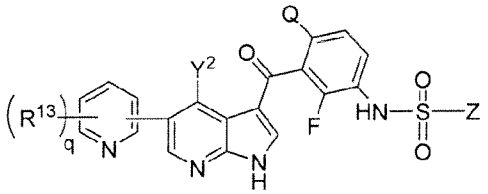
11. The compound of claim **8**, having formula (Id-3):



Id-3

wherein R^7 and R^8 are each independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or $-X^2R^9$, wherein the aliphatic or aromatic portion of R^7 and R^8 are each optionally substituted with from 1 to 3 members independently selected from the group consisting of C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and R^e, provided at each occurrence, at least two of the R^6, R^7 and R^8 groups are not simultaneously hydrogen; and wherein X^2 is $-NR^{10}$, O or S; R^{10} is H, C_{1-6}alkyl or aryl; and R^9 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, wherein R^9 is optionally substituted with from 1 to 3 R^e substituents.

12. The compound of claim **1**, having formula (Ie):



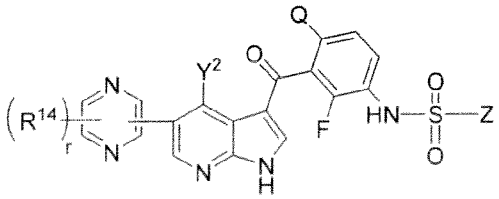
Ie

wherein

R^{13} is H or R^1; or two adjacent R^{13} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; and

the subscript q is an integer of 1 to 4.

13. The compound of claim **1**, having formula (If):



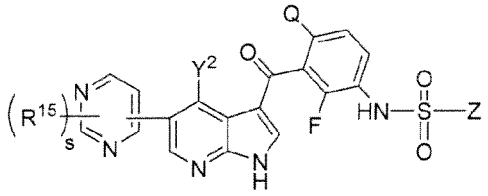
If

wherein

R^{14} is H or R^1; or two adjacent R^{14} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; and

the subscript r is an integer of 1 to 3.

14. The compound of claim **1**, having formula (Ig):



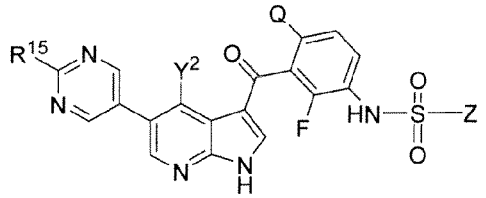
Ig

wherein

R^{15} is H or R^1; or two adjacent R^{15} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; and

the subscript s is an integer of 1 to 3.

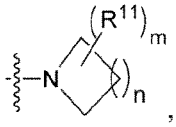
15. The compound of claim **14**, having formula (Ig-1):



Ig-1

16. The compound of claim **14** or **15**, wherein Z is $-N(R^4)(R^5)$.

17. The compound of claim **14** or **15**, wherein Z is:



,

wherein R^{11} is C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or R^e;

the subscript m is an integer from 0 to 3;

the subscript n is an integer from 1 to 5; and the wavy line indicates the point of attachment to the SO_2 group of formulas Ig or Ig-1.

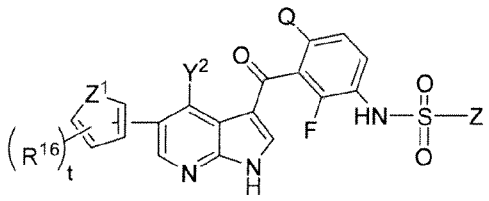
18. The compound of claim **14** or **15**, wherein:

Z is $-CH(R^7)(R^8)$; and

R^7 and R^8 are each independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or $-X^2R^9$, wherein the aliphatic

or aromatic portion of R^7 and R^8 are each optionally substituted with from 1 to 3 members independently selected from the group consisting of C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and R^e, provided at each occurrence, at least two of the R^6, R^7 and R^8 groups are not simultaneously hydrogen; and wherein X^2 is $-NR^{10}$, O or S; R^{10} is H, C_{1-6}alkyl or aryl; and R^9 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, wherein R^9 is optionally substituted with from 1 to 3 R^e substituents.

19. The compound of claim **1**, having formula (Ih):



Ih

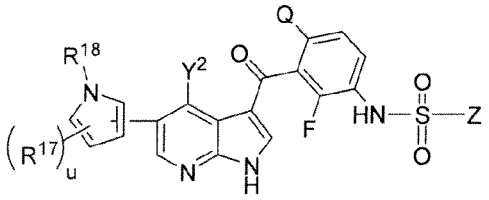
wherein

Z^1 is O or S;

R^{16} is H or R^1; or two adjacent R^{16} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; and

the subscript t is an integer of 1 to 3.

20. The compound of claim **1**, having formula (Ii):



Ii

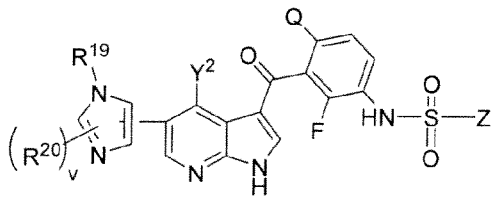
wherein

R^{17} is H or R^1; or two adjacent R^{17} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; or R^{17} and R^{18} taken together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S;

R^{18} is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl or C_{3-6}cycloalkyl; and

the subscript u is an integer of 1 to 3.

21. The compound of claim **1**, having formula (Ij):



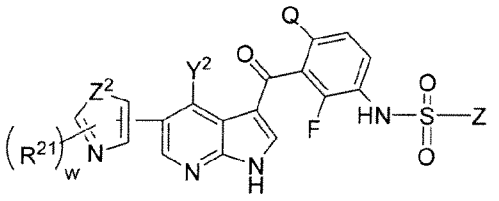
Ij

R^{20} is H or R^1; or two adjacent R^{20} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S; or R^{20} and R^{19} taken together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S;

R^{19} is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl or C_{3-6}cycloalkyl; and

the subscript v is an integer of 1 or 2.

22. The compound of claim **1**, having formula (Ik):



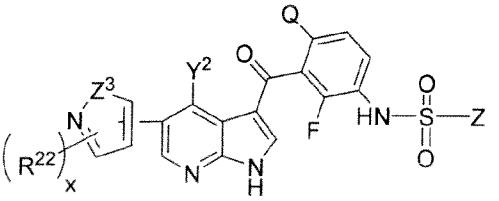
Ik

R^{21} is H or R^1; or two adjacent R^{21} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S;

Z^2 is O or S; and

the subscript w is an integer of 1 or 2.

23. The compound of claim **1**, having formula (Il):



Il

R^{22} is H or R^1; or two adjacent R^{22} together with the atoms to which they are attached form a 5 to 6-membered ring having 0-2 heteroatoms as ring members selected from O, N or S;

Z^3 is O, S or $-N(R^{30})$, wherein R^{30} is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl or C_{3-6}cycloalkyl; and

the subscript x is an integer of 1 or 2.

24. The compound of any of claims **1-7**, wherein Y^1 is selected from the group consisting of phenyl and naphthyl, each of which is independently optionally substituted with from 1-3 R^1 groups, wherein the aromatic portion of R^1 is optionally substituted with from 1-3 substituents independently selected from R^e; or two adjacent R^1 groups on the phenyl or naphthyl ring together with the atoms to which they are attached form a 5- or 6-membered ring having from 0 to 2 additional heteroatoms selected from N, O or S, optionally substituted with from 1 to 3 R^d substituents.

25. The compound of any of claims **1-7**, wherein Y^1 is 5 or 6-membered heteroaryl, each of which is optionally independently substituted with from 1-3 R^1 groups, wherein the aromatic portion of R^1 is optionally substituted with from 1-3 substituents independently selected from R^e; or two adjacent R^1 groups on the phenyl or naphthyl ring together with the atoms to which they are attached form a 5- or 6-membered ring having from 0 to 2 additional heteroatoms selected from N, O or S, optionally substituted with from 1 to 3 R^d substituents.

26. The compound of claim **24** or **25**, wherein each R^1 is independently selected from halogen, -CN, -OH, $-CF_3$, CF_3O-, C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}cycloalkoxy, $-NO_2$, benzyl, phenyl, cyclopropyl, cyclopropylmethyl, 1-cycanocyclopropyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl, 1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cycloheyloxy, C_{1-6}alkyl-1,2,4-oxadiazol-3-yl, 5-C_{1-6}alkyl-1,3,4-oxadiazol-2yl, 5-di(C_{1-6}alkyl)amino-1,3,4-oxadiazol-2yl, 5-C_{1-6}alkylamino-1,3,4-thiadiazol-2-yl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexymethyl, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ or $-NR^bR^b$.

27. The compound of claim **26**, wherein R^1 is F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, C_2H_5O-, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl, 1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cycloheyloxy, 4-morpholino, 4-hydroxypiperidinyl,1- piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-t-butoxycarbonylpiperazinyl, azetidinyl, pyrrolidinyl, cyclopropylcarbamoyl, 5-methyl-1,2,4-oxadiazol-3-yl, 5-methyl-1,3,4-oxadiazol-2yl, 5-dimethylamino-1,3,4-oxadiazol-2yl, 5-methylamino-1,3,4-thiadiazol-2-yl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl.

28. The compound of any of claims **1**, and **3-7**, wherein Y^1 is CN, halogen, -OH, CH_3, CH_3O-, CF_3, CF_3O, cyclopropyl or cyclopropylmethyl.

039363-7211

29. The compound of any of claims **1-7**, wherein (i) Y^1 is selected from the group consisting of 5-pyrimidinyl, 2-pyrimidinyl, 4-pyrimidinyl, 2-methoxy-5-pyrimidinyl, 2-methoxy-3-pyrimidinyl, 2-methoxy-4-pyrimidinyl, 4-methoxy-2-pyrimidinyl, 4-methoxy-4-pyrimidinyl, 4-methoxy-5-pyrimidinyl, 5-methoxy-2-pyrimidinyl, 5-methoxy-4-pyrimidinyl, 2-cyclopropyl-5-pyrimidinyl, 2-cyclopropyl-3-pyrimidinyl, 2-cyclopropyl-4-pyrimidinyl, 4-cyclopropyl-2-pyrimidinyl, 4-cyclopropyl-4-pyrimidinyl, 4-cyclopropyl-5-pyrimidinyl, 5-cyclopropyl-2-pyrimidinyl, 5-cyclopropyl-4-pyrimidinyl, 2-cyclopropylmethyl-5-pyrimidinyl, 2-cyclopropylmethyl-3-pyrimidinyl, 2-cyclopropylmethyl-4-pyrimidinyl, 4-cyclopropylmethyl-2-pyrimidinyl, 4-cyclopropylmethyl-4-pyrimidinyl, 4-cyclopropylmethyl-5-pyrimidinyl, 5-cyclopropylmethyl-2-pyrimidinyl, 5-cyclopropylmethyl-4-pyrimidinyl, 2-methyl-5-pyrimidinyl, 2-methyl-3-pyrimidinyl, 2-methyl-4-pyrimidinyl, 4-methyl-2-pyrimidinyl, 4-methyl-4-pyrimidinyl, 4-methyl-5-pyrimidinyl, 5-methyl-2-pyrimidinyl, 5-methyl-4-pyrimidinyl, 2-halo-5-pyrimidinyl, 2-halo-3-pyrimidinyl, 2-halo-4-pyrimidinyl, 4-halo-2-pyrimidinyl, 4-halo-4-pyrimidinyl, 4-halo-5-pyrimidinyl, 5-halo-2-pyrimidinyl, 5-halo-4-pyrimidinyl, 2-(1-cyanocyclopropyl)-5-pyrimidinyl, 2-(1-cyanocyclopropyl)-3-pyrimidinyl, 2-(1-cyanocyclopropyl)-4-pyrimidinyl, 4-(1-cyanocyclopropyl)-2-pyrimidinyl, 4-(1-cyanocyclopropyl)-4-pyrimidinyl, 4-(1-cyanocyclopropyl)-5-pyrimidinyl, 5-(1-cyanocyclopropyl)-2-pyrimidinyl, 5-(1-cyanocyclopropyl)-4-pyrimidinyl, 2-cyclopropylamino-5-pyrimidinyl, 2-cyclopropylamino-3-pyrimidinyl, 2-cyclopropylamino-4-pyrimidinyl, 4-cyclopropylamino-2-pyrimidinyl, 4-cyclopropylamino-4-pyrimidinyl, 4-cyclopropylamino-5-pyrimidinyl, 5-cyclopropylamino-2-pyrimidinyl, 5-cyclopropylamino-4-pyrimidinyl, 2-dimethylamino-5-pyrimidinyl, 2-dimethylamino-3-pyrimidinyl, 2-dimethylamino-4-pyrimidinyl, 4-dimethylamino-2-pyrimidinyl, 4-dimethylamino-4-pyrimidinyl, 4-dimethylamino-5-pyrimidinyl, 5-dimethylamino-2-pyrimidinyl, 5-dimethylamino-4-pyrimidinyl, 2-cyano-5-pyrimidinyl, 2-cyano-3-pyrimidinyl, 2-cyano-4-pyrimidinyl, 4-cyano-2-pyrimidinyl, 4-cyano-4-pyrimidinyl, 4-cyano-5-pyrimidinyl, 5-cyano-2-pyrimidinyl, 5-cyano-4-pyrimidinyl, 2-trifluoromethyl-5-pyrimidinyl, 2-trifluoromethyl-3-pyrimidinyl, 2-trifluoromethyl-4-pyrimidinyl, 4-trifluoromethyl-2-pyrimidinyl, 4-trifluoromethyl-4-pyrimidinyl, 4- trifluoromethyl-5-pyrimidinyl, 5-trifluoromethyl-2-pyrimidinyl, 5-trifluoromethyl-4-pyrimidinyl, 2-trifluoromethoxy-5-pyrimidinyl, 2-trifluoromethoxy-3-pyrimidinyl, 2-trifluoromethoxy-4-pyrimidinyl, 4-trifluoromethoxy-2-pyrimidinyl, 4-trifluoromethoxy-4-pyrimidinyl, 4-trifluoromethoxy-5-pyrimidinyl, 5-trifluoromethoxy-2-pyrimidinyl, 5-trifluoromethoxy-4-pyrimidinyl, 2-hydroxy-5-pyrimidinyl, 2-hydroxy-3-pyrimidinyl, 2-hydroxy-4-pyrimidinyl, 4-hydroxy-2-pyrimidinyl, 4-hydroxy-4-pyrimidinyl, 4-hydroxy-5-pyrimidinyl, 5-hydroxy-2-pyrimidinyl, 5-hydroxy-4-pyrimidinyl, 2-amino-5-pyrimidinyl, 2-amino-3-pyrimidinyl, 2-amino-4-pyrimidinyl, 4-amino-2-pyrimidinyl, 4-amino-4-pyrimidinyl, 4-amino-5-pyrimidinyl, 5-amino-2-pyrimidinyl, 5-amino-4-pyrimidinyl, 2-methylamino-5-pyrimidinyl, 2-methylamino-3-pyrimidinyl, 2-methylamino-4-pyrimidinyl, 4-methylamino-2-pyrimidinyl, 4-methylamino-4-pyrimidinyl, 4-methylamino-5-pyrimidinyl, 5-methylamino-2-pyrimidinyl, 5-

methylamino-4-pyrimidinyl, 2-dimethylamino-5-pyrimidinyl, 2-dimethylamino-3-pyrimidinyl, 2-dimethylamino-4-pyrimidinyl, 4-dimethylamino-2-pyrimidinyl, 4-dimethylamino-4-pyrimidinyl, 4-dimethylamino-5-pyrimidinyl, 5-dimethylamino-2-pyrimidinyl, 5-dimethylamino-4-pyrimidinyl, 2-acetamido-5-pyrimidinyl, 2-acetamido-3-pyrimidinyl, 2-acetamido-4-pyrimidinyl, 4-acetamido-2-pyrimidinyl, 4-acetamido-4-pyrimidinyl, 4-acetamido-5-pyrimidinyl, 5-acetamido-2-pyrimidinyl, 5-acetamido-4-pyrimidinyl, 2-methylthio-5-pyrimidinyl, 2-methylthio-3-pyrimidinyl, 2-methylthio-4-pyrimidinyl, 4-methylthio-2-pyrimidinyl, 4-methylthio-4-pyrimidinyl, 4-methylthio-5-pyrimidinyl, 5-methylthio-2-pyrimidinyl, 5-methylthio-4-pyrimidinyl, 2-acetoxy-5-pyrimidinyl, 2-acetoxy-3-pyrimidinyl, 2-acetoxy-4-pyrimidinyl, 4-acetoxy-2-pyrimidinyl, 4-acetoxy-4-pyrimidinyl, 4-acetoxy-5-pyrimidinyl, 5-acetoxy-2-pyrimidinyl, 5-acetoxy-4-pyrimidinyl, 2-acetyl-5-pyrimidinyl, 2-acetyl-3-pyrimidinyl, 2-acetyl-4-pyrimidinyl, 4-acetyl-2-pyrimidinyl, 4-acetyl-4-pyrimidinyl, 4-acetyl-5-pyrimidinyl, 5-acetyl-2-pyrimidinyl, 5-acetyl-4-pyrimidinyl, 2-methoxycarbonyl-5-pyrimidinyl, 2-methoxycarbonyl-3-pyrimidinyl, 2-methoxycarbonyl-4-pyrimidinyl, 4-methoxycarbonyl-2-pyrimidinyl, 4-methoxycarbonyl-4-pyrimidinyl, 4-methoxycarbonyl-5-pyrimidinyl, 5-methoxycarbonyl-2-pyrimidinyl, 5-methoxycarbonyl-4-pyrimidinyl, 2-methylcarbamoyl-5-pyrimidinyl, 2-methylcarbamoyl-3-pyrimidinyl, 2-methylcarbamoyl-4-pyrimidinyl, 4-methylcarbamoyl-2-pyrimidinyl, 4-methylcarbamoyl-4-pyrimidinyl, 4-methylcarbamoyl-5-pyrimidinyl, 5-methylcarbamoyl-2-pyrimidinyl, 5-methylcarbamoyl-4-pyrimidinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 3-methoxy-2-pyridyl, 4-methoxy-2-pyridyl, 5-methoxy-2-pyridyl, 6-methoxy-2-pyridyl, 2-methoxy-3-pyridyl, 4-methoxy-3-pyridyl, 5-methoxy-3-pyridyl, 6-methoxy-3-pyridyl, 2-methoxy-4-pyridyl, 3-methoxy-4-pyridyl, 3-halo-2-pyridyl, 4-halo-2-pyridyl, 5-halo-2-pyridyl, 6-halo-2-pyridyl, 2-halo-3-pyridyl, 4-halo-3-pyridyl, 5-halo-3-pyridyl, 6-halo-3-pyridyl, 2-halo-4-pyridyl, 3-halo-4-pyridyl, 3-cyano-2-pyridyl, 4-cyano-2-pyridyl, 5-cayno-2-pyridyl, 6-cyano-2-pyridyl, 2-cyano-3-pyridyl, 4-cyano-3-pyridyl, 5-cyano-3-pyridyl, 6-cyano-3-pyridyl, 2-cyano-4-pyridyl, 3-cyano-4-pyridyl, 3-hydroxy-2-pyridyl, 4-hydroxy-2-pyridyl, 5-hydroxy-2-pyridyl, 6-hydroxy-2-pyridyl, 2-hydroxy-3-pyridyl, 4-hydroxy-3-pyridyl, 5-hydroxy-3-pyridyl, 6-hydroxy-3-pyridyl, 2-hydroxy-4-pyridyl, 3-hydroxy-4-pyridyl, 3-trifluoromethyl-2-pyridyl, 4-trifluoromethyl-2-pyridyl, 5-trifluoromethyl-2-pyridyl, 6-trifluoromethyl-2-pyridyl, 2-trifluoromethyl-3-pyridyl, 4-trifluoromethyl-3-pyridyl, 5-trifluoromethyl-3-pyridyl, 6-trifluoromethyl-3-pyridyl, 2-trifluoromethyl-4-pyridyl, 3-trifluoromethyl-4-pyridyl, 3-amino-2-pyridyl, 4-amino-2-pyridyl, 5-amino-2-pyridyl, 6-amino-2-pyridyl, 2-amino-3-pyridyl, 4-amino-3-pyridyl, 5-amino-3-pyridyl, 6-amino-3-pyridyl, 2-amino-4-pyridyl, 3-amino-4-pyridyl, 3-trifluoromethoxy-2-pyridyl, 4-trifluoromethoxy-2-pyridyl, 5-trifluoromethoxy-2-pyridyl, 6-trifluoromethoxy-2-pyridyl, 2-trifluoromethoxy-3-pyridyl, 4-trifluoromethoxy-3-pyridyl, 5-trifluoromethoxy-3-pyridyl, 6-trifluoromethoxy-3-pyridyl, 2-trifluoromethoxy-4-pyridyl, 3-trifluoromethoxy-4-pyridyl, 3-methyl-2-pyridyl, 4-methyl-2-pyridyl, 5-methyl-2-pyridyl, 6-methyl-2-pyridyl, 2-methyl-3-pyridyl, 4-methyl-3-pyridyl, 5-methyl-3-pyridyl, 6-methyl-3-pyridyl, 2-methyl-4-

pyridyl, 3-methyl-4-pyridyl, 3-methoxy-2-pyridyl, 4-methoxy-2-pyridyl, 5-methoxy-2-pyridyl, 6-methoxy-2-pyridyl, 2-methoxy-3-pyridyl, 4-methoxy-3-pyridyl, 5-methoxy-3-pyridyl, 6-methoxy-3-pyridyl, 2-methoxy-4-pyridyl, 3-methoxy-4-pyridyl, 3-cyclopropyl-2-pyridyl, 4-cyclopropyl-2-pyridyl, 5-cyclopropyl-2-pyridyl, 6-cyclopropyl-2-pyridyl, 2-cyclopropyl-3-pyridyl, 4-cyclopropyl-3-pyridyl, 5-cyclopropyl-3-pyridyl, 6-cyclopropyl-3-pyridyl, 2-cyclopropyl-4-pyridyl, 3-cyclopropyl-4-pyridyl, 3-cyclopropylmethyl-2-pyridyl, 4-cyclopropylmethyl-2-pyridyl, 5-cyclopropylmethyl-2-pyridyl, 6-cyclopropylmethyl-2-pyridyl, 2-cyclopropylmethyl-3-pyridyl, 4-cyclopropylmethyl-3-pyridyl, 5-cyclopropylmethyl-3-pyridyl, 6-cyclopropylmethyl-3-pyridyl, 2-cyclopropylmethyl-4-pyridyl, 3-cyclopropylmethyl-4-pyridyl, 3-cyclopropylamino-2-pyridyl, 4-cyclopropylamino-2-pyridyl, 5-cyclopropylamino2-pyridyl, 6-cyclopropylamino-2-pyridyl, 2-cyclopropylamino-3-pyridyl, 4-cyclopropylamino-3-pyridyl, 5-cyclopropylamino-3-pyridyl, 6-cyclopropylamino-3-pyridyl, 2-cyclopropylamino-4-pyridyl, 3-cyclopropylamino-4-pyridyl, 3-cyclopropylmethylamino-2-pyridyl, 4-cyclopropylmethylamino-2-pyridyl, 5-cyclopropylmethylamino-2-pyridyl, 6-cyclopropylmethylamino-2-pyridyl, 2-cyclopropylmethylamino-3-pyridyl, 4-cyclopropylmethylamino-3-pyridyl, 5-cyclopropylmethylamino-3-pyridyl, 6-cyclopropylmethylamino-3-pyridyl, 2-cyclopropylmethylamino-4-pyridyl, 3-cyclopropylmethylamino-4-pyridyl, 3-methylamino-2-pyridyl, 4-methylamino-2-pyridyl, 5-methylamino-2-pyridyl, 6-methylamino-2-pyridyl, 2-methylamino-3-pyridyl, 4-methylamino-3-pyridyl, 5-methylamino-3-pyridyl, 6-methylamino-3-pyridyl, 2-methylamino-4-pyridyl, 3-methylamino-4-pyridyl, 3-dimethylamino-2-pyridyl, 4-dimethylamino-2-pyridyl, 5-dimethylamino-2-pyridyl, 6-dimethylamino-2-pyridyl, 2-dimethylamino-3-pyridyl, 4-dimethylamino-3-pyridyl, 5-dimethylamino-3-pyridyl, 6-dimethylamino-3-pyridyl, 2-dimethylamino-4-pyridyl, 3-dimethylamino-4-pyridyl, 3-methylthio-2-pyridyl, 4-methylthio-2-pyridyl, 5-methylthio-2-pyridyl, 6-methylthio-2-pyridyl, 2-methylthio-3-pyridyl, 4-methylthio-3-pyridyl, 5-methylthio-3-pyridyl, 6-methylthio-3-pyridyl, 2-methylthio-4-pyridyl, 3-methylthio-4-pyridyl, 3-acetoxy-2-pyridyl, 4-acetoxy-2-pyridyl, 5-acetoxy-2-pyridyl, 6-acetoxy-2-pyridyl, 2-acetoxy-pyridyl, 4-acetoxy-3-pyridyl, 5-acetoxy-3-pyridyl, 6-acetoxy-3-pyridyl, 2-acetoxy-4-pyridyl, 3-acetoxy-4-pyridyl, 3-acetyl-2-pyridyl, 4-acetyl-2-pyridyl, 5-acetyl-2-pyridyl, 6-acetyl-2-pyridyl, 2-acetyl-pyridyl, 4-acetyl-3-pyridyl, 5-acetyl-3-pyridyl, 6-acetyl-3-pyridyl, 2-acetyl-4-pyridyl, 3-acetyl-4-pyridyl, 3-methoxycarbonyl-2-pyridyl, 4-methoxycarbonyl-2-pyridyl, 5-methoxycarbonyl-2-pyridyl, 6-methoxycarbonyl-2-pyridyl, 2-methoxycarbonyl-3-pyridyl, 4-methoxycarbonyl-3-pyridyl, 5-methoxycarbonyl-3-pyridyl, 6-methoxycarbonyl-3-pyridyl, 2-methoxycarbonyl-4-pyridyl, 3-methoxycarbonyl-4-pyridyl, 3-methylcarbamoyl-2-pyridyl, 4-methylcarbamoyl-2-pyridyl, 5-methylcarbamoyl-2-pyridyl, 6-methylcarbamoyl-2-pyridyl, 2-methylcarbamoyl-3-pyridyl, 4-methylcarbamoyl-3-pyridyl, 5-methylcarbamoyl-3-pyridyl, 6-methylcarbamoyl-3-pyridyl, 2-methylcarbamoyl-4-pyridyl, 3-methylcarbamoyl-4-pyridyl, 3-acetamido-2-pyridyl, 4-acetamido-2-pyridyl, 5-acetamido-2-pyridyl, 6-acetamido-2-pyridyl, 2-acetamido-3-pyridyl, 4-acetamido-3-pyridyl, 5-

acetamido-3-pyridyl, 6-acetamido-3-pyridyl, 2-acetamido-4-pyridyl and 3-acetamido-4-pyridyl, 3-(1-cyanocyclopropyl)-2-pyridyl, 4-(1-cyanocyclopropyl)-2-pyridyl, 5-(1-cyanocyclopropyl)-2-pyridyl, 6-(1-cyanocyclopropyl)-2-pyridyl, 2-(1-cyanocyclopropyl)-3-pyridyl, 4-(1-cyanocyclopropyl)-3-pyridyl, 5-(1-cyanocyclopropyl)-3-pyridyl, 6-(1-cyanocyclopropyl)-3-pyridyl and 2-(1-cyanocyclopropyl)-4-pyridyl, 3-(1-cyanocyclopropyl)-4-pyridyl, each of which is optionally substituted with from 1 to 2 susbtituents independently selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, 1-cyanocyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido or methylcarbamoyl; or (ii)Y^1 is selected from the group consisting of 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2- thiophenyl, 3-thiophenyl, 2-amino-quinazolin-5-yl, 2-amino-quinazolin-6-yl, 2-amino-quinazolin-6-yl, 2-amino-quinazolin-7-yl, 2-amino-quinazolin-8-yl, 2-oxo-6-indolinyl, 2-oxo-4-indolinyl, 2-oxo-5-indolinyl, 2-oxo-7-indolinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1H-indazol-4-yl, 1H-indazol-5-yl, 1H-indazol-6-yl and 1H-indazol-7-yl, each of which is substituted with from 1 to 2 susbtituents independently selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, C_2H_5O-, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl, 1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cycloheyloxy, 4-morpholino, 4-hydroxypiperidinyl,1- piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-t-butoxycarbonylpiperazinyl, azetidinyl, pyrrolidinyl, cyclopropylcarbamoyl, 5-methyl-1,2,4-oxadiazol-3-yl, 5-methyl-1,3,4-oxadiazol-2yl, 5-dimethylamino-1,3,4-oxadiazol-2yl, 5-methylamino-1,3,4-thiadiazol-2-yl, methylamino methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl.

30. The compound of any of claims **1-7**, wherein (i) Y^1 is selected from the group consisting of phenyl, 2-halophenyl, 3-halophenyl, 4-halophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-aminophenyl, 3-aminophenyl, 4-aminophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-cyclopropylphenyl, 3-cyclopropylphenyl, 4-cyclopropylphenyl, 2-cyclopropylmethylphenyl, 3- cyclopropylmethylphenyl, 4-cyclopropylmethylphenyl, 2-cyclopropylmethylaminophenyl, 3- cyclopropylmethylaminophenyl, 4-cyclopropylmethylaminophenyl, 2-cyclopropylaminophenyl, 3-cyclopropylaminophenyl, 4-cyclopropylaminophenyl, 2-methylaminophenyl, 3-methylaminophenyl, 4-methylaminophenyl, 2-dimethylaminophenyl, 3-dimethylaminophenyl, 4-dimethylaminophenyl, 2-methylthiophenyl, 3-methylthiophenyl, 4-

methylthiophenyl, 2-acetoxyphenyl, 3-acetoxyphenyl, 4-acetoxyphenyl, 2-acetylphenyl, 3-acetylphenyl, 4-acetylphenyl, 2-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methoxycarbonylphenyl, 2-acetamidophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 2-methylcarbamoylphenyl, 3-methylcarbamoylphenyl, 4-methylcarbamoylphenyl, 2-(1-cyanocyclopropyl)phenyl, 3-(1-cyanocyclopropyl)phenyl and 4-(1-cyanocyclopropyl)phenyl, each of which is optionally substituted with from 1 to 2 susbtituents independently selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, 1-cyanocyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido or methylcarbamoyl; or (ii) Y^1 is phenyl substituted with from 1 to 2 susbtituents independently selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, C_2H_5O-, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, 1-carboxycyclopropyl, 1-carbamoylcyclopropyl, 1-methoxycarbonylcyclopropyl, 1-cyanoisopropyl, 1-hydroxycyclopropyl, 1-hydoxyisopropyl, cyclobutoxy, cyclopentoxy, cycloheyloxy, 4-morpholino, 4-hydroxypiperidinyl, 1-piperidinyl, 1-piperazinyl, 4-methylpiperazinyl, 4-t-butoxycarbonylpiperazinyl, azetidinyl, pyrrolidinyl, cyclopropylcarbamoyl, 5-methyl-1,2,4-oxadiazol-3-yl, 5-methyl-1,3,4-oxadiazol-2yl, 5-dimethylamino-1,3,4-oxadiazol-2yl, 5-methylamino-1,3,4-thiadiazol-2-yl, methylamino methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, isopropyl, 1-pyrrolidinyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylethylamino, 2-cyclopropylethylamino or 1-hydroxy-1-methylethyl.

31. The compound of any of claims **1-23**, wherein Y^2 is H, halogen, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}cycloalkylamino, C_{3-6}cycloalkyl-C_{1-3}alkylamino, aryl, heteroaryl, arylalkyl or heteroarylalkyl.

32. The compound of claim **30**, wherein Y^2 is H, F, Cl, I, CN, CH_3, CH_3O-, cyclopropylamino or cyclopropylmethylamino.

33. The compound of any of claims **1-5**, **8-9**, **12-16** and **19-23**, wherein R^4 and R^5 are each independently selected from C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, aryl-C_{1-4}alkyl, heteroaryl or heteroaryl-C_{1-4}alkyl, each of which is optionally substituted with from 1-3 substituents independently selected from C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or R^e.

34. The compound of any of claims **1-5**, **8-9**, **12-16** and **19-23**, wherein R^4 is $-CH_3$ and R^5 is C_{2-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, aryl-C_{1-4}alkyl, heteroaryl or heteroaryl-C_{1-4}alkyl, each of which is optionally substituted with from 1-3 substituents independently selected from C_{1-}

$_{6}$alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or R^e.

35. The compound of claim **33**, wherein R^4 and R^5 are each independently selected from CH_3, ethyl, propyl, butyl, pentyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, phenyl or benzyl, each of which is optionally substituted with from 1-3 substituents independently selected from F, Cl, Br, I, -CN, -OH, -CF_3, NH_2, CF_3O-, CH_3-, CH_3O, -NO_2, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-oxetanyl, 3-oxtetanyl, 2-oxetanylmethyl, 3-oxtetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 4-morpholinyl, 2-morpholinyl or 3-morpholinyl.

36. The compound of claim **33**, wherein R^4 is CH_3 and R^5 is selected from ethyl, propyl, butyl, pentyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, phenyl or benzyl, each of which is optionally substituted with from 1-3 substituents independently selected from F, Cl, Br, I, -CN, -OH, -CF_3, NH_2, CF_3O-, CH_3-, CH_3O, -NO_2, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido, methylcarbamoyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-oxetanyl, 3-oxtetanyl, 2-oxetanylmethyl, 3-oxtetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 4-morpholinyl, 2-morpholinyl or 3- morpholinyl.

37. The compound of any of claims **1-4**, **8-9**, **12-16** and **19-23**, wherein Z is selected from the group consisting of cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, cycloheptyl, cyclooctyl, 1-azetindinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 4-thiomorpholinyl 3-oxazolidinyl, 3-thiazolidinyl, 2-isoxazolidinyl, 2-isothiazolidinyl, 1-pyrazolidinyl, 1-piperazinyl, 1-hexahydropyrimidinyl and 1-hexahydropyridazinyl, each of which is optionally substituted with from one to three R^{24} substituents independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and R^e; or two adjacent R^{24} substituents together with the atom to which they are attached form a 5 or 6-membered aromatic ring having from 0 to 2 additional atoms as ring members selected from O, N or S.

38. The compound of any of claims **1-4**, **8-9**, **12-16** and **19-23**, wherein Z is selected from the group consisting of 1-pyrrolidinyl, sec-butyl, pentan-2-yl, pentan-3-yl, cyclopropyl, $(CH_3)(CF_3CH_2)N$-, cycloproylmethylamino, cyclobutyl and cyclopentyl, each of which is optionally substituted with from 1-2 members selected from -F, methoxycarbonyl, ethoxycarbonyl, $-CH_3$, $CH_3(CO)NH$-, vinyl, propen-3-yl or $CH_3(CO)(CH_3)N$-.

39. The compound of any of claims **6**, **10**, and **17**, wherein n is 1, 2, 3 or 4.

40. The compound of any of claims **6**, **10**, and **17**, wherein the subscript m is 0.

41. The compound of any of claims **6**, **10**, and **17**, wherein R^{11} is H, F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, phenyl, benzyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, ethyoxycarbonyl, acetamido, methylcarbamoyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-oxetanyl, 3-oxtetanyl, 2-oxetanylmethyl, 3-oxtetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 4-morpholinyl, 2-morpholinyl, 3- morpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-thiophenyl, 3-thiophenyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl or 2-thiazoly.

42. The compound of any of claims **9-23**, wherein R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from H, CN, halogen, -OH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-4}alkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl, heteroaryl and heterocycloalkyl, wherein the aliphatic or aromatic portion of R^{12} is further optionally substituted with from 1-3 substituents selected from F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, benzyl, beznzyloxy, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido or methylcarbamoyl.

43. The compound of claim **42**, wherein R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from H, F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, cyclopropyl, cyclopropylmethyl, cyclopropylamino, cyclopropylmethylamino, 1-cyanocyclopropyl, benzyl, methylamino, dimethylamino, methylthio, acetoxy, acetyl, methoxycarbonyl, acetamido or methylcarbamoyl.

039363-7211

44. A compound selected from any of compounds P-0012 to P-0117 and P-0223 to P-0351 as set forth in Table 2 or pharmaceutically acceptable salts, hydrates, solvates, tautomers and isomers thereof.

45. A compound selected from any of compounds P-0118 to P-0222 as set forth in Table 3 or pharmaceutically acceptable salts, hydrates, solvates, tautomers and isomers thereof.

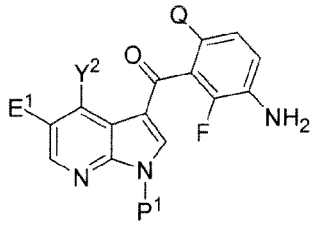
46. A composition comprising a compound of any of claims **1-45** and a pharmaceutically acceptable excipient or carrier.

47. A composition comprising a compound of any of claims **1-45** and another therapeutic agent.

48. A kit comprising a compound of any of claims **1-45.**

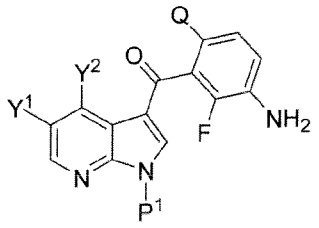
49. A method for preparing a compound of formula (I) according to claim **1**, said method comprising:

contacting a compound having formula II:

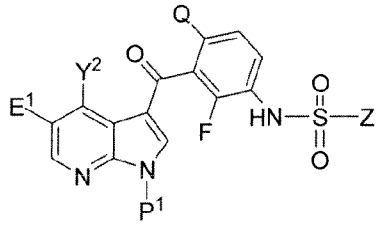


II

with an agent of formula (III): Y^1-G^1 or formula (IV): A^1-$S(O)_2$-Z (IV) under conditions sufficient to form a compound having formulas (V) or (VI):



or



(V) (VI)

reacting (i) a compound of formula (V) with a compound of formula (IV), or (ii) a compound of formula (VI) with an agent of formula (III) under conditions sufficient to form the compound of formula (I); wherein said contacting or reacting with the agent of formula (III) is in the presence of a palladium complex; and wherein

E^1 is halogen, tosylate or mesylate;

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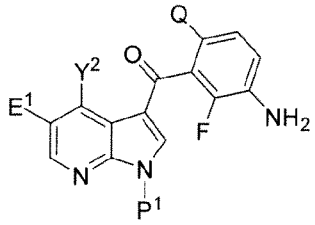
G^1 is $-B(OR^{25})_2$ or $-Sn(Bu)_3$, wherein R^{25} is –OH, alkyl or two $-OR^{25}$ substituents together with the boron atom to which they are attached to form an optionally substituted 5 or 6-membered ring;

A^1 is a leaving group; and

P^1 is H or an amino protecting group.

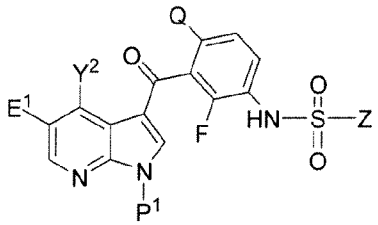
50. A method for preparing a compound of formula (I) according to claim **1**, said method comprising:

reacting a compound having formula II:



II

with a compound of formula (IV): A^1-$S(O)_2$-Z under conditions sufficient to form a compound having formula (VI):



(VI)

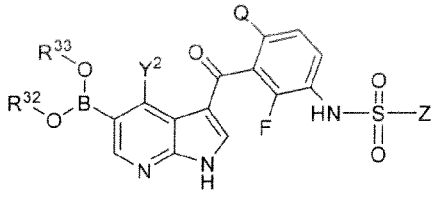
reacting a compound of formula (VI) with a compound of the formula: Y^1-E^2 and a compound of the formula: $(OR^{31})_2B$-$B(OR^{31})_2$ in the presence of a palladium complex under conditions sufficient to form the compound of formula (I), wherein R^{31} is –OH, alkyl or two $-OR^{31}$ substituents together with the boron atom to which they are attached to form a 5 or 6-membered ring; and wherein

E^1 and E^2 are each independently halogen, tosylate or mesylate;

A^1 is a leaving group; and

P^1 is H or an amino protecting group.

51. A compound having formula (VIII):



VIII

wherein R^{32} and R^{33} are each independently H, optionally substituted alkyl, optionally substituted arylalkyl or optionally substituted aryl;

Y^2, Q and Z are defined as in any of claims **1-45**.

52. A method for treating a subject suffering from or at risk of a protein kinase mediated diseases or conditions, said method comprising:

administering to said subject an effective amount of a compound of any of claims **1-45** or a composition of any of claims **46** or **47**.

53. The method of claim **52**, wherein the protein kinase is B-Raf and any mutations thereof.

54. The method of claim **52**, wherein said disease or condition is selected from the group consisting of ischemic stroke, cerebrovascular ischemia, multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, dementia, senile chorea, Huntington's disease, neoplastic disease, complications with neoplastic disease, chemotherapy-induced hypoxia, gastrointestinal stromal tumors, prostate tumors, mast cell tumors, canine mast cell tumors, acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, melanoma, mastocytosis, glioma, glioblastoma, astrocytoma, neuroblastoma, sarcomas, sarcomas of neuroectodermal origin, leiomyosarcoma, lung carcinoma, breast carcinoma, pancreatic carcinoma, colon carcinoma, hepatocellular carcinoma, renal carcinoma, carcinoma of the female genital tract, squamous cell carcinoma, carcinoma in situ, lymphoma, histiocytic lymphoma, non-Hodgkin's lymphoma, MEN2 syndromes, neurofibromatosis, Schwann cell neoplasia, myelodysplastic syndrome, leukemia, tumor angiogenesis, thyroid cancer, liver cancer, bone cancer, skin cancer, brain cancer, cancer of the central nervous system, pancreatic cancer, lung cancer, small cell lung cancer, non small cell lung cancer, breast cancer, colon cancer, bladder cancer, prostate cancer, gastrointestinal tract cancer, cancer of the endometrium, fallopian tubecancer, testicular cancer, ovarian cancer, pain of neuropathic origin, pain of inflammatory origin, acute pain, chronic pain, migraine, cardiovascular disease, heart failure, cardiac hypertrophy, thrombosis, thrombotic microangiopathy syndromes, atherosclerosis, reperfusion injury, ischemia, cerebrovascular ischemia, liver ischemia, inflammation, polycystic kidney disease, age-related macular degeneration, rheumatoid arthritis, allergic rhinitis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, Wegener's granulomatosis, psoriasis, scleroderma, chronic thyroiditis, Grave's disease, myasthenia gravis, multiple sclerosis, osteoarthritis, endometriosis, dermal scarring, tissue scarring, vascular restenosis, fibrotic disorders, hypereosinophilia, CNS inflammation, pancreatitis, nephritis, atopic dermatitis, hepatitis, immunodeficiency diseases, severe combined immunodeficiency,

organ transplant rejection, graft versus host disease, renal disease, prostatic disease, diabetic nephropathy, nephrosclerosis, glomerulonephritis, interstitial nephritis, Lupus nephritis, prostate hyperplasia, chronic renal failure, tubular necrosis, diabetes-associated renal complication, associated renal hypertrophy, type 1 diabetes, type 2 diabetes, metabolic syndrome, obesity, hepatic steatosis, insulin resistance, hyperglycemia, lipolysis obesity, infection, *Helicobacter pylori* infection, *Influenza virus* infection, fever, sepsis, pulmonary diseases, chronic obstructive pulmonary disease, acute respiratory distress syndrome, asthma, allergy, bronchitis, emphysema, pulmonary fibrosis, genetic developmental diseases, Noonan's syndrome, Crouzon syndrome, acrocephalo-syndactyly type I, Pfeiffer's syndrome, Jackson-Weiss syndrome, Costello syndrome, faciocutaneoskeletal syndrome, leopard syndrome, cardio-faciocutaneous syndrome, neural crest syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair or endocrine diseases, disorders of bone structure or mineralization, osteoporosis, increased risk of fracture, hypercalcemia, bone metastases, Grave's disease, Hirschsprung's disease, lymphoedema, selective T-cell defect, X-linked agammaglobulinemia, diabetic retinopathy, alopecia, erectile dysfunction, and tuberous sclerosis.

55. The method of claim **54**, wherein said disease or condition is selected from melanomer, thyroid or colon cancer.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/023543

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/407 (2012.01)
USPC - 514/300
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) -A61K 31/407; C07D 209/00, 221/00 (2012.01)
USPC - 514/255.05, 300; 546/113

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 practicable, search terms used)
PatBase, Orbit, SureChemOpen, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0249118 A1 (IBRAHIM et al) 30 September 2010 (30.09.2010) entire document	1-5, 7-9, 11, 12, 19, 20 24, 25, 28, 44, 45
X	US 2010/0286178 A1 (IBRAHIM et al) 11 November 2010 (11.11.2010) entire document	1, 6
X ---- Y	WO 2010/129570 A1 (VISOR et al) 11 November 2010 (11.11.2010) entire document This document can be viewed by entering the doc number at the following url: http://worldwide.espacenet.com/numberSearch?locale=en_EP	1, 8, 10, 13-18, 21-23, 29, 30, 32, 49 ---------- 50
Y	WO 2010/059658 A1 (AXTEN et al) 27 May 2010 (27.05.2010) entire document This document can be viewed by entering the doc number at the following url: http://worldwide.espacenet.com/numberSearch?locale=en_EP	50

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

* 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 application or patent 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	Date of mailing of the international search report
30 April 2012	31 MAY 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/023543

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.: 26, 27, 31, 33-43, 46-48, 51-55
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:

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 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.

COMPUESTOS Y MÉTODOS PARA LA MODULACIÓN DE QUINASAS E INDICACIONES PARA LOS MISMOS

RESUMEN

Se describen compuestos activos en las proteína quinasas así como métodos de preparación y uso de dichos compuestos para tratar enfermedades y estados vinculados con actividad aberrante de las proteína quinasas.

COMPUESTOS Y MÉTODOS PARA LA MODULACIÓN DE QUINASAS E INDICACIONES PARA LOS MISMOS

CAMPO DE LA INVENCIÓN

[0001] La presente invención se relaciona con quinasas y compuestos que modulan selectivamente las quinasas y sus usos. Las realizaciones particulares contemplan indicaciones de enfermedades susceptibles de tratamiento a través de la modulación de la actividad de quinasa mediante los compuestos de la presente invención.

ANTECEDENTES DE LA INVENCIÓN

[0002] Las proteína quinasas receptoras regulan las cascadas de transducción de señales claves que controlan o participan en el control de una plétora de funciones fisiológicas entre las cuales se incluye crecimiento y proliferación celular, diferenciación celular, desarrollo celular, división celular, adhesión celular, reacción al estrés, guía axónica mediada por contacto

de corto alcance, regulación de transcripción, mitogénesis aberrante, angiogénesis, interacciones anormales endoteliales célula a célula o célula a matriz durante el desarrollo vascular, inflamación, actividad linfohematopoyética de células troncales, inmunidad protectora contra bacterias específicas, asma alérgica, reacciones aberrantes específicas de tejidos a la activación de la ruta de transducción de señales JNK, transformación celular, memoria, apoptosis, modificación de sinapsis dependientes de actividad competitiva en la sinapsis neuromuscular, mediación inmunológica de la enfermedad y regulación del calcio.

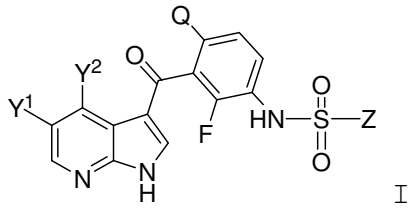
[0003] Las enfermedades específicas vinculadas con la regulación aberrante de proteína quinasas incluyen, por ejemplo, no taxativamente, acrocefalosindactilia tipo I, leucemia mieloide aguda, linfoma no Hodgkin inducido por SIDA, enfermedad de Alzheimer, esclerosis lateral amiotrófica, artritis, asma, ateroesclerosis, dermatitis atópica, enfermedades autoinmunes, infección bacteriana, cáncer de vejiga, cáncer de mama, cáncer del sistema nervioso central, cáncer del colon, cáncer del endometrio, cáncer de las trompas de Falopio, cáncer del tracto gastrointestinal, cáncer del ovario, insuficiencia cardiaca, leucemia mieloide crónica, carcinoma de colon, cáncer colorrectal, enfermedad pulmonar obstructiva crónica (COPD), Síndrome de Crouzon, diabetes, nefropatía diabética, enfisema, endometriosis, cáncer epidermoide, trastornos fibróticos, tumor estromal gastrointestinal (GIST), glomerulonefritis, Enfermedad de Gra-

ves, lesión de cabeza, carcinoma hepatocelular, Enfermedad de Hirschsprung, gliomas humanos, enfermedades provocadas por inmunodeficiencia, trastornos inflamatorios, ataque isquémico, Síndrome de Jackson-Weiss, leiomiosarcoma, leucemias, nefritis lúpica, melanoma maligno, nefroesclerosis maligna, mastocitosis, tumores de mastocitos, melanoma del colon, Síndromes MEN2, trastornos metabólicos, migraña, esclerosis múltiple, trastornos mieloproliferativos, nefritis, enfermedades neurodegenerativas, enfermedades neurotraumáticas, cáncer pulmonar de células no pequeñas, rechazo a transplante de órganos, osteoporosis, dolor, Enfermedad de Parkinson, Síndrome de Pfeiffer, enfermedad renal policística, linfoedema primario, cáncer de la próstata, soriasis, restenosis vascular, artritis reumatoidea, cicatrización dérmica y de tejidos, defecto selectivo en las células T (STD), inmunodeficiencia combinada grave (SCID), cáncer pulmonar de células pequeñas, lesión de la médula espina, carcinoma de células escamosas, lupus eritematoso sistémico, cáncer testicular, síndromes de microangiopatía trombótica, granulomatosis de Wegener, Agammaglobulinemia congénita, infección viral, retinopatía diabética, alopecia, disfunción eréctil, degeneración macular, leucemia linfocítica crónica (CLL), síndrome mielodisplásico (MDS), neurofibromatosis y esclerosis tuberosa. Por lo tanto, existe una necesidad de la tecnología de contar con compuestos y métodos de uso de los mismos para la modulación de proteína qui-

nasas receptoras. La presente invención satisface estas y otras enfermedades.

RESUMEN DE LA INVENCIÓN

[0004] En un aspecto, la presente invención proporciona un compuesto de fórmula I:



I

y sales, hidratos, solvatos, tautómeros e isómeros de los mismos aceptables farmacéuticamente;

donde:

Y^1 se selecciona del grupo que consiste en CN, halógeno, -OH, C_{1-6} alquilo sustituido opcionalmente, C_{1-6} alcoxi sustituido opcionalmente, C_{3-6}cicloalquilo sustituido opcionalmente, C_{1-6} haloalquilo sustituido opcionalmente, C_{1-6} haloalcoxi sustituido opcionalmente, arilo sustituido opcionalmente y heteroarilo sustituido opcionalmente; opcionalmente donde dos sustituyentes adyacentes sobre un arilo sustituido o un anillo de heteroarilo sustituido junto con los átomos a los cuales están unidos forman un anillo de 5 o 6 miembros sustituido opcionalmente que tiene de 0 a 3 heteroátomos adicionales seleccionados de N, O o S;

Y^2 es H, halógeno, CN, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, C_{3-8} cicloalquilo-C_{0-4} alquilo o $(R^2)(R^3)$ N-, donde

R^2 y R^3 son seleccionados cada uno por separado del grupo que consiste en H, C_{1-6} alquilo, C_{1-6} alcoxi, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, C_{3-8} cicloalquilo-C_{0-4} alquilo, heterocicloalquilo y heterocicloalquilo-C_{1-4} alquilo; o R^2 y R^3 tomados junto con el átomo de nitrógeno al cual están unidos forman un anillo de tres a ocho miembros que tiene de 0-2 heteroátomos adicionales como miembros de anillo seleccionados de N, O o S; donde Y^2 es sustituido opcionalmente con uno a tres grupos seleccionados por separado de R^e;

Q es seleccionado de H, F, Cl o CH_3;

Z es $-N(R^4)(R^5)$ o $-C(R^6)(R^7)(R^8)$, donde

R^4 y R^5 son seleccionados cada uno por separado del grupo que consiste en H, sustituido opcionalmente C_{1-6} alquilo, sustituido opcionalmente C_{3-8} cicloalquilo, sustituido opcionalmente C_{3-8} cicloalquiloalquilo, sustituido opcionalmente heterocicloalquilo, sustituido opcionalmente heterocicloalquiloalquilo, sustituido opcionalmente arilo, sustituido opcionalmente ariloalquilo, sustituido opcionalmente heteroarilo y sustituido opcionalmente heteroariloalquilo; o R^4 y R^5 tomados junto con el átomo de nitrógeno al cual están unidos forman un anillo de cuatro a ocho miembros que tiene de 0-2 heteroátomos adicionales como miembros de anillo seleccionados de N, O o S, donde el anillo de cuatro a ocho miembros es sustituido opcionalmente;

R^6, R^7 y R^8 son cada uno por separado H, C_{1-6} alquilo sustituido opcionalmente, , C_{1-6} haloalquilo sustituido opcionalmente, C_{1-6} haloalcoxi sustituido opcionalmente, C_{3-8} cicloalquilo sustituido opcionalmente, C_{3-8} cicloalquiloalquilo sustituido opcionalmente, arilo sustituido opcionalmente, ariloalquilo sustituido opcionalmente, heterociclo-alquilo sustituido opcionalmente, heterocicloalquiloalquilo sustituido opcionalmente, heteroarilo sustituido opcionalmente, heteroariloalquilo o $-X^2R^9$ sustituido opcionalmente, donde X^2 es $-NR^{10}$, O o S; R^{10} es H, C_{1-6} alquilo o arilo; y R^9 es H, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, C_{3-8} cicloalquilo, C_{3-8} cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo o heteroariloalquilo, donde R^9 es sustituido opcionalmente con 1 a 3 sustituyentes R^e; o

dos opciones cualesquiera de los grupos R^6, R^7 y R^8 tomados junto con el átomo de carbono al cual están unidos forma un anillo no aromático de 3 a 8 miembros sustituido opcionalmente que tiene de 0 a 2 heteroátomos seleccionados de N, O o S; proporcionado en cada aparición, como mínimo dos opciones cualesquiera de los grupos R^6, R^7 y R^8 no son simultáneamente hidrógeno; y en el entendido de que (i) Y^1 es halógeno, $-CH_3$, -CN, -OMe o 2-metoxipirimidin-5-il, Z es otro aparte de dimetilamino, dietilamino, 1-pirrolodina, 1-piperidinilo, 4-morfolinilo, isopropilo, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_3)(CH_2CH_2CH_3)$, ciclobutilo, ciclopentilo o ciclohexilo;

y (ii) cuando Y^1 es 1-metil-4-pirazolilo, 3-metilsulfonilfenilo o 3-metilsulfonilaminofenilo, Z es otro aparte de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo.

[0005] En algunas realizaciones,

Y^1 es CN, halógeno, -OH, C_{1-6} alquilo, C_{1-6} alcoxi, sustituido opcionalmente C_{3-6}cicloalquilo, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, arilo y heteroarilo, donde la porción alifática o aromática de Y^1 es cada una por separado sustituida opcionalmente con 1-5 R^1 sustituyentes;

cada R^1 es seleccionado por separado de C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, C_{3-8} cicloalquilo, C_{3-8} cicloalquilo-C_{1-4}-alquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, heterocicloalquilo, heterocicloalquilo-C_{1-4} alquilo o $-R^a$, donde R^a es seleccionado de halógeno, $-CH=CH_2$, -CN, -OH, $-NH_2$, $-NO_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^b$, $-SR^b$, $-OC(O)R^b$, $-OC(S)R^b$, $-C(O)R^b$, $-C(S)R^b$, $-C(O)OR^b$, $-C(S)OR^b$, $-S(O)R^b$, $-S(O)_2R^b$, $-C(O)NHR^b$, $-C(S)NHR^b$, $-C(O)NR^bR^b$, $-C(S)NR^bR^b$, $-S(O)_2NHR^b$, $-S(O)_2NR^bR^b$, $-C(NH)NHR^b$, $-C(NH)NR^bR^b$, $-NHC(O)R^b$, $-NHC(S)R^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NHS(O)_2R^b$, $-NR^bS(O)_2R^b$, $-NHC(O)NHR^b$, $-NHC(S)NHR^b$, $-NR^bC(O)NH_2$, $-NR^bC(S)NH_2$, $-NR^bC(O)NHR^b$, $-NR^bC(S)NHR^b$, $-NHC(O)NR^bR^b$, $-NHC(S)NR^bR^b$, $-NR^bC(O)NR^bR^b$, $-NR^bC(S)NR^bR^b$, $-NHS(O)_2NHR^b$, $-NR^bS(O)_2NH_2$, $-NR^bS(O)_2NHR^b$, $-NHS(O)_2NR^bR^b$, $-NR^bS(O)_2NR^bR^b$, $-NHR^b$ o $-NR^bR^b$,

cada R^b es seleccionado por separado del grupo que consiste en C_{1-6} alquilo, halógeno, –CN, C_{1-6} alcoxi, C_{3-8} cicloalquilo, C_{3-8} cicloalquilo–C_{1-4}–alquilo, –OH, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, arilo, arilo–C_{1-4} alquilo, heteroarilo y heteroariloalquilo; o dos sustituyentes R^b cuando están unidos al mismo átomo de nitrógeno tomados junto con el átomo de nitrógeno forman un anillo de tres a ocho miembros que tiene de 0–2 heteroátomos adicionales como miembros de anillo seleccionados de N, O o S; donde la porción alifática o aromática de R^1 es sustituida opcionalmente además con 1–3 grupos seleccionados de C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, heterocicloalquilo, heterocicloalquilo–C_{1-4}alquilo o $-R^c$,

cada R^c es seleccionado por separado de halógeno, –CN, –OH, $-CH=CH_2$, $-NH_2$, $-NO_2$, $-C(O)OH$, $-C(S)OH$, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^d$, $-SR^d$, $-OC(O)R^d$, $-OC(S)R^d$, $-C(O)R^d$, $-C(S)R^d$, $-C(O)OR^d$, $-C(S)OR^d$, $-S(O)R^d$, $-S(O)_2R^d$, $-C(O)NHR^d$, $-C(S)NHR^d$, $-C(O)NR^dR^d$, $-C(S)NR^dR^d$, $-S(O)_2NHR^d$, $-S(O)_2NR^dR^d$, $-C(NH)NHR^d$, $-C(NH)NR^dR^d$, $-NHC(O)R^d$, $-NHC(S)R^d$, $-NR^dC(O)R^d$, $-NR^dC(S)R^d$, $-NHS(O)_2R^d$, $-NR^dS(O)_2R^d$, $-NHC(O)NHR^d$, $-NHC(S)NHR^d$, $-NR^dC(O)NH_2$, $-NR^dC(S)NH_2$, $-NR^dC(O)NHR^d$, $-NR^dC(S)NHR^d$, $-NHC(O)NR^dR^d$, $-NHC(S)NR^dR^d$, $-NR^dC(O)NR^dR^d$, $-NR^dC(S)NR^dR^d$, $-NHS(O)_2NHR^d$, $-NR^dS(O)_2NH_2$, $-NR^dS(O)_2NHR^d$, $-NHS(O)_2NR^dR^d$, $-NR^dS(O)_2NR^dR^d$, $-NHR^d$, R^f o $-NR^dR^d$,

cada R^d es seleccionado por separado de C_{1-6}alquilo, ariloalquilo, arilo, heteroarilo, heteroariloalquilo, cicloalquilo, cicloalquiloalquilo, heterocicloalquilo o heterocicloalquiloalquilo; y donde la porción aromática de R^1 es sustituida opcionalmente con 1–3 sustituyentes seleccionados por separado de R^e,

R^e se selecciona del grupo que consiste en halógeno, –CN, –$CH=CH_2$, –OH, –NH_2, –NO_2, –C(O)OH, –C(S)OH, –$C(O)NH_2$, –$C(S)NH_2$, –$S(O)_2NH_2$, –$NHC(O)NH_2$, –$NHC(S)NH_2$, –$NHS(O)_2NH_2$, –$C(NH)NH_2$, –OR^f, –SR^f, –$OC(O)R^f$, –$OC(S)R^f$, –$C(O)R^f$, –$C(S)R^f$, –$C(O)OR^f$, –$C(S)OR^f$, –$S(O)R^f$, –$S(O)_2R^f$, –$C(O)NHR^f$, –$C(S)NHR^f$, –$C(O)NR^fR^f$, –$C(S)NR^fR^f$, –$S(O)_2NHR^f$, –$S(O)_2NR^fR^f$, –$C(NH)NHR^f$, –$C(NH)NR^fR^f$, –$NHC(O)R^f$, –$NHC(S)R^f$, –$NR^fC(O)R^f$, –$NR^fC(S)R^f$, –$NHS(O)_2R^f$, –$NR^fS(O)_2R^f$, –$NHC(O)NHR^f$, –$NHC(S)NHR^f$, –$NR^fC(O)NH_2$, –$NR^fC(S)NH_2$, –$NR^fC(O)NHR^f$, –$NR^fC(S)NHR^f$, –$NHC(O)NR^fR^f$, –$NHC(S)NR^fR^f$, –$NR^fC(O)NR^fR^f$, –$NR^fC(S)NR^fR^f$, –$NHS(O)_2NHR^f$, –$NR^fS(O)_2NH_2$, –$NR^fS(O)_2NHR^f$, –$NHS(O)_2NR^fR^f$, –$NR^fS(O)_2NR^fR^f$, –NHR^f, –NR^fR^f y R^f,

R^f es C_{1-6}alquilo o arilo; o dos grupos adyacentes R^1 en el anillo de arilo o heteroarilo junto con los átomos a los cuales están unidos forman un anillo de 5 o 6 miembros que tiene de 0 a 2 heteroátomos adicionales seleccionados de N, O o S, sustituido opcionalmente con 1 a 3 sustituyentes R^d;

R^4 y R^5 son seleccionados cada uno por separado del grupo que consiste en H, C_{1-6} alquilo, C_{3-8} cicloalquilo, C_{3-8} cicloalquiloalquilo, heterocicloalquilo, heterocicloalquiloalquilo, arilo, ariloalquilo, heteroarilo y heteroariloalquilo, donde R^4 o

R^5 es sustituido opcionalmente con 1 a 3 miembros seleccionados por separado de C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, C_{1-6} alquilo, C_{3-8} cicloalquilo, C_{3-8} cicloalquiloalquilo, heterociclo-alquilo, heterocicloalquiloalquilo, arilo, ariloalquilo, hete-roarilo, heteroariloalquilo o R^c; o

R^4 y R^5 tomados junto con el átomo de nitrógeno al cual están unidos forman un anillo de cuatro a ocho miembros que tie-ne de 0-2 heteroátomos adicionales como miembros de anillo se-leccionados de N, O o S, donde dicho anillo de cuatro a ocho miembros es sustituido opcionalmente con uno a tres grupos se-leccionados por separado de C_{1-6}haloalquilo, C_{1-6} haloalcoxi, C_{1-6} alquilo, C_{3-8} cicloalquilo, C_{3-8} cicloalquiloalquilo, arilo, ari-loalquilo o R^e; y

R^6, R^7 y R^8 son cada uno por separado H, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, C_{3-8} cicloalquilo, C_{3-8} cicloalquilo-alquilo, arilo, ariloalquilo, heterocicloalquilo, heterocicloal-quiloalquilo, heteroarilo, heteroariloalquilo o $-X^2R^9$; donde la porción alifática o aromática de R^6, R^7 y R^8 es cada una susti-tuida opcionalmente con 1 a 3 miembros seleccionados por separa-do del grupo que consiste en C_{3-8} cicloalquilo, C_{3-8} cicloalquilo-alquilo, arilo, ariloalquilo, heterocicloalquilo, heterocicloal-quiloalquilo, heteroarilo, heteroariloalquilo y R^e; o

dos opciones cualesquiera de los grupos R^6, R^7 y R^8 tomados junto con el átomo de carbono al cual están unidos forman un anillo carbocíclico de 3 a 8 miembros o un anillo heterocíclico

de 4 a 8 miembros que tiene de 1 a 2 heteroátomos como miembros de anillo seleccionados de N, O o S, donde el anillo carbocíclico de 3 a 8 miembros o el anillo heterocíclico de 4 a 8 miembros es sustituido opcionalmente con uno a tres grupos seleccionados por separado de C_{1-6} haloalquilo, C_{1-6} haloalcoxi, C_{1-6} alquilo sustituido opcionalmente con R^e, C_{3-8} cicloalquilo, C_{3-8} cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo o heteroariloalquilo o R^e.

[0006] En otro aspecto, la invención proporciona una composición. La composición incluye un compuesto de cualquiera de las fórmulas I a In, un compuesto conforme a los enumerados en cualquiera de las reivindicaciones y descritos en el presente documento o una sal o solvato del mismo aceptable farmacéuticamente y un excipiente o soporte aceptable farmacéuticamente. La invención también proporciona una composición, la cual incluye un compuesto conforme a los enumerados en las reivindicaciones y descritos en el presente documento, un excipiente o soporte aceptable farmacéuticamente y otro agente terapéutico.

[0007] En otro aspecto adicional, la invención proporciona un equipo, el cual incluye un compuesto de cualquiera de las fórmulas I a In, un compuesto conforme a los enumerados en cualquiera de las reivindicaciones y descritos en el presente documento, o una sal o solvato del mismo aceptable farmacéuticamente. La invención también proporciona un equipo, el cual incluye una composición que comprende un compuesto de fórmulas I a In,

un compuesto conforme a los enumerados en cualquiera de las reivindicaciones y descritos en el presente documento, o una sal o solvato del mismo aceptable farmacéuticamente.

[0008] En otro aspecto, la invención proporciona un método de preparación de un compuesto de fórmula (I) y cualquiera de las fórmulas subgenéricas.

[0009] En otro aspecto adicional, la invención proporciona un método para tratar a un sujeto que padece de una enfermedad o estado mediado por proteína quinasas o presenta un riesgo de padecerlo. El método incluye administrar al sujeto una cantidad eficaz de un compuesto de cualquiera de las fórmulas I a In, un compuesto conforme a los enumerados en cualquiera de las reivindicaciones y descritos en el presente documento, o una sal o solvato del mismo aceptable farmacéuticamente, o una composición que comprende un compuesto de cualquiera de las fórmulas I a In, un compuesto conforme a los enumerados en cualquiera de las reivindicaciones y descritos en el presente documento, o una sal o solvato del mismo aceptable farmacéuticamente.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

I. Definiciones

[0010] Según se usan en el presente documento son pertinentes las definiciones siguientes salvo que se indique claramente de otro modo:

[0011] Cabe destacar en este caso que, según se usan en la presente especificación y las reivindicaciones anexas, las for-

mas singulares "un" “una” y "el" “la” incluyen la referencia plural salvo que el contexto lo indique claramente de otro modo.

[0012] “Halógeno” o “halo” se refiere a todos los halógenos, es decir, cloro (Cl), fluoro (F), bromo (Br) o yodo (I).

[0013] “Hidroxilo” o "hidroxi" se refiere al grupo –OH.

[0014] “Tiol” se refiere al grupo –SH.

[0015] El término "alquilo", por sí mismo o como parte de otro sustituyente, significa, salvo que se indique de otro modo, una cadena de hidrocarburo recta o ramificada, que tiene el número de átomos de carbono designado (*es decir,* C_{1-6} significa uno a seis carbonos). Los grupos alquilo representativos incluyen grupos alquilo de cadena recta o ramificada que tienen 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 o 12 átomos de carbono. Otros grupos alquilo representativos incluyen grupos alquilo de cadena recta o ramificada que tienen 1, 2, 3, 4, 5, 6, 7 u 8 átomos de carbono. Los ejemplos de grupos alquilo incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, t-butilo, isobutilo, sec-butilo, n-pentilo, n-hexilo, n-heptilo, n-octilo y otros semejantes. Para cada una de las definiciones proporcionadas en el presente documento (p. ej., alquilo, alcoxi, alquiloamino, alquiltio, alquileno, haloalquilo, ariloalquilo, cicloalquiloalquilo, heterocicloalquiloalquilo, heteroariloalquilo), cuando no se incluye un prefijo para indicar el número de átomos de carbono en una porción de alquilo, la molécula de alquilo o porción de la misma tendrá 12 o menos átomos de carbono de cadena principal u 8 o

menos átomos de carbono de cadena principal o 6 o menos átomos de carbono de cadena principal. Por ejemplo, C_{1-8} alquilo se refiere a un hidrocarburo recto o ramificado que tiene 1, 2, 3, 4, 5 o 6 átomos de carbono e incluye, no taxativamente, C_{1-2} alquilo, C_{1-4} alquilo, C_{2-6} alquilo, C_{2-4} alquilo, C_{1-6} alquilo, C_{2-8} alquilo, C_{1-7} alquilo, C_{2-7} alquilo y C_{3-6} alquilo. “Alquilo fluoro sustituido” denota un grupo alquilo sustituido con uno o más átomos de flúor, como por ejemplo perfluoroalquilo, donde preferiblemente el alquilo inferior es sustituido con 1, 2, 3, 4 o 5 átomos de flúor, también 1, 2, o 3 átomos de flúor. Si bien se entiende que las sustituciones están unidas a cualquier átomo disponible para producir un compuesto estable, cuando el alquilo sustituido opcionalmente es un grupo R de una molécula como por ejemplo –O (p.ej. alcoxi), –SR (p.ej. tioalquilo), –NHR (p.ej. alquiloamino), –C(O)NHR y otros semejantes, la sustitución del grupo R será aquella en la cual la sustitución del alquilo carbono unido a cualquier O, S, o N del fragmento (excepto en los casos donde N es un átomo de anillo de heteroarilo) excluye sustituyentes que conduciría a que cualquiera de O, S, o N del sustituyente (excepto en los casos donde N es un átomo de anillo de heteroarilo) se una al alquilo carbono unido a cualquiera O, S, o N del fragmento.

[0016] El término "alquileno" por sí mismo o como parte de otro sustituyente significa una fracción de hidrocarburo divalente saturado lineal o ramificado derivada de un alcano que

tiene el número de átomos de carbono indicado en el prefijo. Por ejemplo, (es decir, C_{1-6} significa uno a seis carbonos; C_{1-6} alquileno significa que está incluido metileno, etileno, propileno, 2-metilpropileno, pentileno, hexileno y otros semejantes). C_{1-4} alquileno incluye metileno $-CH_2-$, etileno $-CH_2CH_2-$, propileno $-CH_2CH_2CH_2-$ y isopropileno $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-CH_2-(CH_2)_2CH_2-$, $-CH_2-CH(CH_3)CH_2-$, $-CH_2-C(CH_3)_2-$, $-CH_2-CH_2CH(CH_3)-$. Normalmente, un grupo alquilo (o alquileno) tendrá 1 a 24 átomos de carbono, con siendo preferidos aquellos grupos que tienen 10 o menos, 8 o menos, o 6 o menos átomos de carbono en la presente invención. Cuando no se incluye un prefijo para indicar el número de átomos de carbono en una porción de alquileno, la fracción de alquileno o porción de la misma tendrá 12 o menos átomos de carbono de cadena principal u 8 o menos átomos de carbono de cadena principal, 6 o menos átomos de carbono de cadena principal o 4 o menos átomos de carbono de cadena principal.

[0017] El término "alquenileno" se refiere a una fracción de hidrocarburo bivalente lineal o una molécula de hidrocarburo monovalente ramificada que tiene el número de átomos de carbono indicado en el prefijo y que contiene como mínimo una unión doble. Por ejemplo, es decir, C_{2-6} significa dos a seis carbonos; C_{2-6} alquenileno significa que está incluido, no taxativamente, $-CH=CH-$, $-CH_2-CH=CH-$, $-CH_2-CH=C(CH_3)-$, $-CH=CH-CH=CH-$ y otros semejantes). De manera semejante, el término "alquinileno" se refiere a una fracción de hidrocarburo bivalente lineal o una molécu-

la de hidrocarburo monovalente ramificada que contiene como mínimo una unión triple y que tiene el número de átomos de carbono indicado en el prefijo. Por ejemplo, (es decir, C_{2-6} significa dos a seis carbonos; C_{2-6} alquinileno significa que está incluido, no taxativamente, $-C\equiv C-$, $-C\equiv CCH_2-$, $-CH_2-C\equiv CCH_2-$, $-C\equiv CCH(CH_3)-$ y otros semejantes. Cuando no se incluye un prefijo para indicar el número de átomos de carbono en una alquenileno o porción de alquinileno, la fracción de alquenileno o porción de la misma tendrá 12 o menos átomos de carbono de cadena principal u 8 o menos átomos de carbono de cadena principal o 6 o menos átomos de carbono de cadena principal o 4 o menos átomos de carbono de cadena principal.

[0018] "Cicloalquilo" por sí mismo o como parte de otro sustituyente, se refiere a sistemas de anillos de carbono saturado o no saturado, no aromático monocíclico, bicíclico o tricíclico de 3-10, también 3-8, más preferiblemente 3-6, miembros de anillo por anillo, como por ejemplo ciclopropilo, ciclopentilo, ciclohexilo, 1-ciclohexenilo, adamantilo y otros semejantes. Cicloalquilo se refiere a anillos de hidrocarburo que tienen el número indicado de átomos de anillo (*p. ej.*, C_{3-8} cicloalquilo significa tres a ocho átomos de carbono de anillo)

[0019] "Cicloalquiloalquilo" se refiere a un grupo -(alquileno)-cicloalquilo donde el alquileno, según se define en el presente documento, tiene el número indicado de átomos de carbono o de no estar especificado tiene seis o menos, preferi-

blemente cuatro o menos átomos de carbono de cadena principal; y cicloalquilo, según se define en el presente documento, tiene el número indicado de átomos de carbono. C_{3-8}cicloalquiloalquilo significa que tiene 3 a 8 átomos de carbono de anillo. Entre los cicloalquiloalquilos ejemplo se incluye, p. ej., ciclopropilmetiloeno, ciclobutiloetileno, ciclobutilometileno y otros semejantes.

[0020] "Haloalquilo," significa que está incluido alquilo sustituido por uno a siete átomos de halógeno. Haloalquilo incluye monohaloalquilo y polihaloalquilo. Por ejemplo, el término "C_{1-6} haloalquilo" significa que está incluido trifluorometilo, difluorometilo, 2,2,2-trifluoroetilo, 4-clorobutilo, 3-bromopropilo y otros semejantes.

[0021] "Haloalcoxi" se refiere a un grupo –O-haloalquilo, donde haloalquilo tiene la definición dada en el presente documento, p.ej., trifluorometoxi, 2,2,2-trifluoroetoxi, difluorometoxi y otros semejantes.

[0022] "Alcoxi" se refiere a un grupo –O-alquilo, donde alquilo tiene la definición dada en el presente documento. "Cicloalcoxi" se refiere a un grupo –O-cicloalquilo, donde cicloalquilo tiene la definición dada en el presente documento. "Alcoxi fluoro sustituido" denota alcoxi en el cual el alquilo es sustituido con uno o más átomos de flúor, donde preferiblemente el alcoxi es sustituido con 1, 2, 3, 4 o 5 átomos de flúor, también 1, 2, o 3 átomos de flúor. Si bien se da por entendido que las

sustituciones en alcoxi están unidas a cualquier átomo disponible para producir un compuesto estable, la sustitución de alcoxi es aquella en la cual O, S, o N (excepto en los casos donde N es un átomo de anillo de heteroarilo), no están unidos al alquilo carbono unido al alcoxi O. Adicionalmente, donde aparece alcoxi descrito como un sustituyente de otra molécula, el oxígeno del alcoxi no está unido a un átomo de carbono es decir unido a un O, S, o N de la otra molécula (excepto en los casos donde N es un átomo de anillo de heteroarilo) o a un alqueno o alquino carbono de la otra fracción.

[0023] "Amino" o "amina" denota el grupo $-NH_2$.

[0024] "Alquiloamino" se refiere a un grupo –NH–alquilo, donde alquilo tiene la definición dada en el presente documento. Los grupos alquiloamino ejemplo incluyen CH_3NH–, etilamino y otros semejantes.

[0025] "Dialquiloamino" se refiere a un grupo –N(alquilo)(alquilo), donde cada alquilo es por separado según se define en el presente documento. Los grupos dialquiloamino ejemplo incluyen dimetilamino, dietilamino, etilmetilamino y otros semejantes.

[0026] "Cicloalquiloamino" denota el grupo $-NR^{dd}R^{ee}$, donde R^{dd} y R^{ee} se combinan con el nitrógeno para producir un anillo de heterocicloalquilo de 5-7 miembros, donde el heterocicloalquilo puede contener un heteroátomo adicional dentro del anillo, como por ejemplo O, N, o S, y puede también ser sustituido además con

alquilo. De manera alternativa, “cicloalquiloamino” se refiere a un grupo –NH–cicloalquilo, donde cicloalquilo tiene la definición dada en el presente documento.

[0027] “Alquiltio” se refiere a –S–alquilo, donde alquilo tiene la definición dada en el presente documento. Los grupos alquiltio ejemplo incluyen CH_3S–, etiltio y otros semejantes.

[0028] “Arilo” por sí mismo o como parte de otro sustituyente se refiere a una fracción de hidrocarburo poliinsaturado monocíclico, bicíclico o policíclico que contiene 6 a 14 átomos de carbono de anillo. Los ejemplos no taxativos de grupos arilo no sustituidos incluyen fenilo, 1–naftilo, 2–naftilo y 4–bifenilo. Un grupo arilo ejemplo, como por ejemplo fenilo o naftilo, que puede estar opcionalmente fusionado con un cicloalquilo de preferiblemente 5–7, más preferiblemente 5–6, miembros de anillo.

[0029] "Ariloalquilo" se refiere a –(alquileno)–arilo, donde el grupo alquileno tiene la definición dada en el presente documento y tiene el número indicado de átomos de carbono, o de no estar especificado, tiene seis o menos átomos de carbono de cadena principal o cuatro o menos átomos de carbono de cadena principal; y arilo tiene la definición dada en el presente documento. Los ejemplos de ariloalquilo incluyen bencilo, fenetilo y otros semejantes.

[0030] “Heteroarilo” por sí mismo o como parte de otro sustituyente se refiere a una estructura de anillos aromáticos monocíclicos que contiene 5 o 6 átomos de anillo, o un grupo aromá–

tico bicíclico que tiene 8 a 10 átomos, que contiene uno o más, preferiblemente 1-4, más preferiblemente 1-3, incluso más preferiblemente 1-2, heteroátomos seleccionados por separado del grupo que consiste en O, S y N. Heteroarilo pretende incluir también S o N oxidado, como por ejemplo sulfinilo, sulfonilo y N-óxido de un nitrógeno de anillo terciario. Un átomo de carbono o nitrógeno es el punto de unión de la estructura de anillos de heteroarilo de modo que se produce un compuesto estable. Los ejemplos de grupos heteroarilo incluyen, no taxativamente, piridinilo, piridacinilo, piracinilo, indolicinilo, benzo[b]tienilo, quinazolinilo, purinilo, indolilo, quinolinilo, pirimidinilo, pirrolilo, pirazolilo, oxazolilo, tiazolilo, tienilo, isoxazolilo, oxatiadiazolilo, isotiazolilo, tetrazolilo, imidazolilo, triazolilo, furanilo, benzofurilo, indolilo, triacinilo, quinoxalinilo, cinnolinilo, ftalacinilo, benzotriacinilo, benzimidazolilo, benzopirazolilo, benzotriazolilo, benzisoxazolilo, isobenzofurilo, isoindolilo, indolicinilo, benzotriacinilo, tienopiridinilo, tienopirimidinilo, pirazolopirimidinilo, imidazopiridinas, benzotiaxolilo, benzotienilo, quinolilo, isoquinolilo, indazolilo, pteridinilo y tiadiazolilo. “Nitrógeno que contiene heteroarilo” se refiere a heteroarilo donde cualquiera de los heteroátomos es N.

[0031] "Heteroariloalquilo" se refiere a -(alquileno)-heteroarilo, donde el grupo alquileno tiene la definición dada en el presente documento y tiene el número indicado de átomos de

carbono o, de no estar especificado, tiene seis o menos átomos de carbono de cadena principal o cuatro o menos átomos de carbono de cadena principal; y heteroarilo tiene la definición dada en el presente documento. Los ejemplos de heteroariloalquilo incluyen 2-piridilometilo, 2-tiazoliloetilo y otros semejantes.

[0032] "Heterocicloalquilo" se refiere a un grupo cicloalquilo no aromático saturado o no saturado que contiene de uno a cinco heteroátomos seleccionados de N, O y S, donde los átomos de nitrógeno y azufre átomos son oxidados opcionalmente y el (los) átomo (s) de nitrógeno son opcionalmente cuaternizados, siendo los átomos de anillo restantes C, donde uno o dos átomos C pueden ser remplazados opcionalmente por un carbonilo. El heterocicloalquilo puede ser un sistema de anillos monocíclico, a bicíclico o policíclico de 3 a 12, preferiblemente 4 a 10 átomos de anillo, más preferiblemente, 5 a 8 átomos de anillo en el cual uno a cinco átomos de anillo son heteroátomos seleccionados de -N=, -N-, -O-, -S-, -S(O)-, o $-S(O)_2-$ y además donde uno o dos átomos de anillo son remplazados opcionalmente por un grupo -C(O)-. El heterocicloalquilo también puede ser un anillo de alquilo heterocíclico fusionado con un cicloalquilo, un arilo o un anillo heteroarilo. Ejemplos no taxativos de grupos heterocicloalquilo incluyen pirrolidinilo, piperidinilo, imidazolidinilo, pirazolidinilo, fracción de butirolactamo, fracción de valerolactamo, fracción de imidazolidinona, hidantoína, fracción de dioxolano, fracción de ftalimida, piperidina, fracción de 1,4-

dioxano, morfolinilo, tiomorfolinilo, tiomorfolinilo-S-óxido, tiomorfolinilo-S,S- óxido, piperacinilo, piranilo, fracción de piridina, 3-pirrolinilo, tiopiranilo, fracción de pirona, tetrahidrofuranilo, tetrahidrotiofenilo, quinuclidinilo y otros semejantes. Un grupo heterocicloalquilo puede agregarse al resto de la molécula a través de un carbono de anillo o un heteroátomo.

[0033] "Heterocicloalquiloalquilo" se refiere a -(alquileno)-heterocicloalquilo, donde el grupo alquileno tiene la definición dada en el presente documento y tiene el número indicado de átomos de carbono, o de no estar especificado tiene seis o menos átomos de carbono de cadena principal o cuatro o menos átomos de carbono de cadena principal; y heterocicloalquilo tiene la definición dada en el presente documento. Los ejemplos de heterocicloalquiloalquilo incluyen 2-piridilometilo, 2-tiazoliloetilo y otros semejantes.

[0034] Los sustituyentes de alquilo, alcoxi, haloalquilo, haloalcoxi, cicloalquilo, cicloalquiloalquilo, alquileno, alquenileno, alquinileno incluyen, no taxativamente, R', halógeno, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-C(O)OH$, $-C(S)OH$, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-O'$, $-SR'$, $-OC(O)R'$, $-OC(S)R'$, $-C(O)R'$, $-C(S)R'$, $-C(O)O'$, $-C(S)O'$, $-S(O)R'$, $-S(O)_2R'$, $-C(O)NHR'$, $-C(S)NHR'$, $-C(O)NR'R''$, $-C(S)NR'R''$, $-S(O)_2NHR'$, $-S(O)_2NR'R''$, $-C(NH)NHR'$, $-C(NH)NR'R''$, $-NHC(O)R'$, $-NHC(S)R'$, $-NR''C(O)R'$, $-NR'C(S)R''$, $-NHS(O)_2R'$, $-NR'S(O)_2R''$,

$-NHC(O)NHR'$, $-NHC(S)NHR'$, $-NR'C(O)NH_2$, $-NR'C(S)NH_2$, $-NR'C(O)NHR''$, $-NR'C(S)NHR''$, $-NHC(O)NR'R''$, $-NHC(S)NR'R''$, $-NR'C(O)NR''R'''$, $-NR'''C(S)NR'R''$, $-NHS(O)_2NHR'$, $-NR'S(O)_2NH_2$, $-NR'S(O)_2NHR''$, $-NHS(O)_2NR'R''$, $-NR'S(O)_2NR''R'''$, $-NHR'$ y $-NR'R''$ en un número comprendido dentro de la gama de cero a (2m'+1), donde m' es el número total de átomos de carbono en dicho grupo. R', R" y R"' cada uno por separado se refiere a hidrógeno, C_{1-8} alquilo, heterocicloalquilo, arilo, heteroarilo, ariloalquilo, heteroariloalquilo, arilo sustituido con 1-3 halógenos, grupos C_{1-8} alcoxi, haloalquilo, haloalcoxi o C_{1-8} tioalcoxi o grupos no sustituidos arilo-C_{1-4} alquilo. Cuando R' y R" están unidos al mismo átomo de nitrógeno, pueden combinarse con el átomo de nitrógeno para producir un anillo de 3-, 4-, 5-, 6- o 7 miembros. Por ejemplo, -NR'R" significa que está incluido 1-pirrolidinilo y 4-morfolinilo. R', R" y R"' puede sustituirse adicionalmente con R^{a1}, halógeno, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-C(O)OH$, $-C(S)OH$, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^{a1}$, $-SR^{a1}$, $-OC(O)R^{a1}$, $-OC(S)R^{a1}$, $-C(O)R^{a1}$, $-C(S)R^{a1}$, $-C(O)OR^{a1}$, $-C(S)OR^{a1}$, $-S(O)R^{a1}$, $-S(O)_2R^{a1}$, $-C(O)NHR^{a1}$, $-C(S)NHR^{a1}$, $-C(O)NR^{a1}R^{a2}$, $-C(S)NR^{a1}R^{a2}$, $-S(O)_2NHR^{a1}$, $-S(O)_2NR^{a1}R^{a2}$, $-C(NH)NHR^{a1}$, $-C(NH)NR^{a1}R^{a2}$, $-NHC(O)R^{a1}$, $-NHC(S)R^{a1}$, $-NR^{a2}C(O)R^{a1}$, $-NR^{a1}C(S)R^{a2}$, $-NHS(O)_2R^{a1}$, $-NR^{a1}S(O)_2R^{a2}$, $-NHC(O)NHR^{a1}$, $-NHC(S)NHR^{a1}$, $-NR^{a1}C(O)NH_2$, $-NR^{a1}C(S)NH_2$, $-NR^{a1}C(O)NHR^{a2}$, $-NR^{a1}C(S)NHR^{a2}$, $-NHC(O)NR^{a1}R^{a2}$, $-NHC(S)NR^{a1}R^{a2}$, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a3}C(S)NR^{a1}R^{a2}$, $-NHS(O)_2NHR^{a1}$, $-NR^{a1}S(O)_2NH_2$, $-NR^{a1}S(O)_2NHR^{a2}$, $-NHS(O)_2NR^{a1}R^{a2}$, $-NR^{a1}S(O)_2NR^{a2}R^{a3}$,

$-NHR^{a1}$ y $-NR^{a1}R^{a2}$ en un número comprendido dentro de la gama de cero a (2n'+1), donde n' es el número total de átomos de carbono en dicho grupo. R^{a1}, R^{a2} y R^{a3} cada uno por separado se refiere a hidrógeno, grupos C_{1-8} alquilo, heterocicloalquilo, arilo, heteroarilo, ariloalquilo, heteroariloalquilo, arilo sustituido con 1-3 halógenos, C_1-_8 alcoxi, haloalquilo, haloalcoxi o C_1-_8 tioalcoxi o grupos arilo-C_1-_4 alquilo no sustituidos. R^{a1}, R^{a2} y R^{a3} puede sustituirse adicionalmente con R^{b1}, halógeno, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-C(O)OH$, $-C(S)OH$, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^{b1}$, $-SR^{b1}$, $-OC(O)R^{b1}$, $-OC(S)R^{b1}$, $-C(O)R^{b1}$, $-C(S)R^{b1}$, $-C(O)OR^{b1}$, $-C(S)OR^{b1}$, $-S(O)R^{b1}$, $-S(O)_2R^{b1}$, $-C(O)NHR^{b1}$, $-C(S)NHR^{b1}$, $-C(O)NR^{b1}R^{b2}$, $-C(S)NR^{b1}R^{b2}$, $-S(O)_2NHR^{b1}$, $-S(O)_2NR^{b1}R^{b2}$, $-C(NH)NHR^{b1}$, $-C(NH)NR^{b1}R^{b2}$, $-NHC(O)R^{b1}$, $-NHC(S)R^{b1}$, $-NR^{b2}C(O)R^{b1}$, $-NR^{b1}C(S)R^{b2}$, $-NHS(O)_2R^{b1}$, $-NR^{b1}S(O)_2R^{b2}$, $-NHC(O)NHR^{b1}$, $-NHC(S)NHR^{b1}$, $-NR^{b1}C(O)NH_2$, $-NR^{b1}C(S)NH_2$, $-NR^{b1}C(O)NHR^{b2}$, $-NR^{b1}C(S)NHR^{b2}$, $-NHC(O)NR^{b1}R^{b2}$, $-NHC(S)NR^{b1}R^{b2}$, $-NR^{b1}C(O)NR^{b2}R^{b3}$, $-NR^{b3}C(S)NR^{b1}R^{b2}$, $-NHS(O)_2NHR^{b1}$, $-NR^{b1}S(O)_2NH_2$, $-NR^{b1}S(O)_2NHR^{b2}$, $-NHS(O)_2NR^{b1}R^{b2}$, $-NR^{b1}S(O)_2NR^{b2}R^{b3}$, $-NHR^{b1}$ y $-NR^{b1}R^{b2}$ en un número comprendido dentro de la gama de cero a (2p'+1), donde p' es el número total de átomos de carbono en dicho grupo. R^{b1}, R^{b2} y R^{b3} cada uno por separado se refiere a hidrógeno, grupos C_{1-8} alquilo, heterocicloalquilo, arilo, heteroarilo, ariloalquilo, heteroariloalquilo, arilo sustituido con 1-3 halógenos, C_1-_8 alcoxi, haloalquilo, haloalcoxi o C_1-_8 tioalcoxi grupos o grupos arilo-C_1-_4 alquilo no sustituidos.

[0035] Los sustituyentes para arilo y grupos heteroarilo son variados y en general se seleccionan de: R', halógeno, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-C(O)OH$, $-C(S)OH$, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-O'$, $-SR'$, $-OC(O)R'$, $-OC(S)R'$, $-C(O)R'$, $-C(S)R'$, $-C(O)O'$, $-C(S)O'$, $-S(O)R'$, $-S(O)_2R'$, $-C(O)NHR'$, $-C(S)NHR'$, $-C(O)NR'R''$, $-C(S)NR'R''$, $-S(O)_2NHR'$, $-S(O)_2NR'R''$, $-C(NH)NHR'$, $-C(NH)NR'R''$, $-NHC(O)R'$, $-NHC(S)R'$, $-NR''C(O)R'$, $-NR'C(S)R''$, $-NHS(O)_2R'$, $-NR'S(O)_2R''$, $-NHC(O)NHR'$, $-NHC(S)NHR'$, $-NR'C(O)NH_2$, $-NR'C(S)NH_2$, $-NR'C(O)NHR''$, $-NR'C(S)NHR''$, $-NHC(O)NR'R''$, $-NHC(S)NR'R''$, $-NR'C(O)NR''R'''$, $-NR'''C(S)NR'R''$, $-NHS(O)_2NHR'$, $-NR'S(O)_2NH_2$, $-NR'S(O)_2NHR''$, $-NHS(O)_2NR'R''$, $-NR'S(O)_2NR''R'''$, $-NHR'$, $-NR'R''$, $-N_3$, perfluoro (C_1-C_4)alcoxi y perfluoro (C_1-C_4)alquilo, en un número comprendido dentro de la gama de cero al número total de valencias abiertas en el sistema de anillos aromáticos; y donde R', R" y R"' son seleccionados por separado de hidrógeno, haloalquilo, haloalcoxi, C_{1-8} alquilo, C_{3-6} cicloalquilo, cicloalquiloalquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, arilo-C_{1-4} alquilo y arilooxi-C_{1-4} alquilo. Otros sustituyentes adecuados incluyen cada uno de los sustituyentes de arilo anteriores unidos a un átomo de anillo por una unión de alquileno de 1-4 átomos de carbono. R', R" y R"' puede sustituirse adicionalmente con R^{a1}, halógeno, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-C(O)OH$, $-C(S)OH$, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^{a1}$, $-SR^{a1}$, $-OC(O)R^{a1}$,

$-OC(S)R^{a1}$, $-C(O)R^{a1}$, $-C(S)R^{a1}$, $-C(O)OR^{a1}$, $-C(S)OR^{a1}$, $-S(O)R^{a1}$, $-S(O)_2R^{a1}$, $-C(O)NHR^{a1}$, $-C(S)NHR^{a1}$, $-C(O)NR^{a1}R^{a2}$, $-C(S)NR^{a1}R^{a2}$, $-S(O)_2NHR^{a1}$, $-S(O)_2NR^{a1}R^{a2}$, $-C(NH)NHR^{a1}$, $-C(NH)NR^{a1}R^{a2}$, $-NHC(O)R^{a1}$, $-NHC(S)R^{a1}$, $-NR^{a2}C(O)R^{a1}$, $-NR^{a1}C(S)R^{a2}$, $-NHS(O)_2R^{a1}$, $-NR^{a1}S(O)_2R^{a2}$, $-NHC(O)NHR^{a1}$, $-NHC(S)NHR^{a1}$, $-NR^{a1}C(O)NH_2$, $-NR^{a1}C(S)NH_2$, $-NR^{a1}C(O)NHR^{a2}$, $-NR^{a1}C(S)NHR^{a2}$, $-NHC(O)NR^{a1}R^{a2}$, $-NHC(S)NR^{a1}R^{a2}$, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a3}C(S)NR^{a1}R^{a2}$, $-NHS(O)_2NHR^{a1}$, $-NR^{a1}S(O)_2NH_2$, $-NR^{a1}S(O)_2NHR^{a2}$, $-NHS(O)_2NR^{a1}R^{a2}$, $-NR^{a1}S(O)_2NR^{a2}R^{a3}$, $-NHR^{a1}$,$-NR^{a1}R^{a2}$, $-N_3$, perfluoro (C_1-C_4)alcoxi y perfluoro (C_1-C_4)alquilo, en un número comprendido dentro de la gama de cero al número total de valencias abiertas en el sistema de anillos aromáticos; y donde R^{a1}, R^{a2} y R^{a3} son seleccionados cada uno por separado de hidrógeno, haloalquilo, haloalcoxi, C_{1-8} alquilo, C_{3-6} cicloalquilo, cicloalquiloalquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, arilo-C_{1-4} alquilo, o arilooxi-C_{1-4} alquilo. Otros sustituyentes adecuados incluyen cada uno de los sustituyentes de arilo anteriores unidos a un átomo de anillo por una unión de alquileno de 1-4 átomos de carbono.

[0036] Cuando están presentes dos sustituyentes en átomos adyacentes de un arilo sustituido o un anillo de heteroarilo sustituido, dichos sustituyentes pueden ser remplazados opcionalmente con un sustituyente de la fórmula $-T-C(O)-(CH_2)_q-U-$, donde T y U son por separado -NH-, -O-, $-CH_2-$ o una unión sencilla y q es un número entero de 0 a 2. De manera alternativa, cuando

están presentes dos sustituyentes en átomos adyacentes de un arilo sustituido o un anillo de heteroarilo sustituido, dichos sustituyentes pueden ser remplazados opcionalmente con un sustituyente de la fórmula $-A-(CH_2)_r-B-$, donde A y B son por separado $-CH_2-$, $-O-$, $-NH-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2NR'-$ o una unión sencilla y R es un número entero de 1 a 3. Una de las uniones sencillas del anillo nuevo así formado puede ser remplazada opcionalmente por una unión doble. De manera alternativa, cuando están presentes dos sustituyentes en átomos adyacentes de un arilo sustituido o un anillo de heteroarilo sustituido, dichos sustituyentes pueden ser remplazados opcionalmente con un sustituyente de la fórmula $-(CH_2)_s-X-(CH_2)_t-$, donde s y t son por separado números enteros de 0 a 3 y X es $-O-$, $-NR'-$, $-S-$, $-S(O)-$, $-S(O)_2-$, o $-S(O)_2NR'-$. El sustituyente R' en $-NR'-$ y $-S(O)_2NR'-$ es seleccionado de hidrógeno o no sustituido C_{1-6} alquilo.

[0037] "Grupo protector" se refiere a una agrupación de átomos que cuando está unida a un grupo reactivo en una molécula enmascara, reduce o previene dicha reactividad. Los ejemplos de grupos protectores pueden encontrarse en T.W. Greene y P.G. Wuts, PROTECTIVE GROUPS IN ORGANIC CHEMISTRY, (Wiley, 4th ed. 2006), Beaucage y Iyer, *Tetrahedron* 48:2223-2311 (1992) y Harrison y Harrison *et al.*, COMPENDIUM OF SYNTHETIC ORGANIC METHODS, Vols. 1-8 (John Wiley y Sons. 1971-1996). Los grupos amino protectores representativos incluyen grupos formilo, acetilo, trifluoroacetilo, bencilo, benciloxicarbonilo (CBZ), *terc*butoxicarbonilo

(Boc), trimetil sililo (TMS), 2-trimetilsililo-etanosulfonilo (SES), tritilo y grupos tritilo sustituidos, allilooxicarbonilo, 9-fluorenilmetiloxicarbonilo (FMOC), nitro-veratriloxicarbonilo (NVOC), tri-isopropilsililo (TIPS), fenilosulfonilo y otros semejantes (ver también, Boyle, A. L. (Editor), carbamatos, amidas, derivados de N-sulfonilo, grupos de fórmula -C(O)O, donde R es, por ejemplo, metilo, etilo, t-butilo, bencilo, feniloetilo, CH_2=$CHCH_2$- y otros semejantes, grupos de la formula -C(O)R', donde R' es, por ejemplo, metilo, fenilo, trifluorometilo y otros semejantes, grupos de la formula -SO_2R'', donde R'' es, por ejemplo, tolilo, fenilo, trifluorometilo, 2,2,5,7,8-pentametilcroman-6-il, 2,3,6-trimetil-4-metoxifenilo y otros semejantes y silanilo que contiene grupos, como por ejemplo 2-trimetilsililoetoximetilo, t-butildimetilsililo, triisopropilsililo y otros semejantes, CURRENT PROTOCOLS IN NUCLEIC ACID CHEMISTRY, John Wiley y Sons, New York,Volume 1, 2000).

[0038] Según se usan en el presente documento, el término "composición" se refiere a una formulación adecuada de administración a un sujeto animal con fines terapéuticos que contiene como mínimo un compuesto farmacéuticamente activo y como mínimo un soporte o excipiente aceptable farmacéuticamente.

[0039] El término "aceptable farmacéuticamente" indica que el material indicado no posee propiedades que llevarían a un profesional de la medicina razonablemente prudente a evitar la administración del material a un paciente, tomando en cuenta la en-

fermedad o estado a tratar y la respectiva ruta de administración. Por ejemplo, frecuentemente se requiere que dicho material sea esencialmente estéril, p. ej., para los inyectables.

[0040] "Sal aceptable farmacéuticamente" se refiere a una sal aceptable para la administración a un paciente, como por ejemplo un mamífero (p. ej., sales que ofrecen una seguridad aceptable para mamíferos para un régimen de dosis dado). Dichas sales pueden ser derivadas de bases inorgánicas u orgánicas aceptables farmacéuticamente y de ácidos inorgánicos u orgánicos aceptables farmacéuticamente, dependiendo de los sustituyentes particulares presentes en los compuestos descritos en este documento. Cuando los compuestos de la presente contienen funcionalidades relativamente acídicas, se pueden obtener sales de adición de base poniendo en contacto la forma neutra de dichos compuestos con una cantidad suficiente de la base deseada, o bien pura o en un solvente inerte adecuado. Las sales derivadas de bases inorgánicas aceptables farmacéuticamente incluyen aluminio, amonio, calcio, cobre, férricas, ferrosas, litio, magnesio, mangánicas, manganosas, potasio, sodio, zinc y otros semejantes. Las sales derivadas de bases orgánicas aceptables farmacéuticamente incluyen sales de aminas primarias, secundarias, terciarias y cuaternarias, incluyendo aminas sustituidas, aminas cíclicas, aminas presentes en la naturaleza y otros semejantes, como por ejemplo arginina, betaína, cafeína, colina, N, N'- dibenciloetilenodiamina, dietilamina, 2-dietilaminoetanol, 2- dimetilaminoetanol, etanolamina,

etilenodiamina, N-etilmorfolina, N- etilpiperidina, glucamina, glucosamina, histidina, hidrabamina, isopropilamina, lisina, metilglucamina, morfolina, piperacina, piperidina, resinas de poliamina, procaína, purinas, teobromina, trietilamina, trimetilamina, tripropilamina, trometamina y otros semejantes. Cuando los compuestos de la presente invención contienen funcionalidades relativamente básicas, las sales de adición de ácido pueden obtenerse poniendo en contacto la forma neutra de dichos compuestos con una cantidad suficiente del ácido deseado, o bien puro o en un solvente inerte adecuado. La sales derivadas de ácido aceptables farmacéuticamente incluyen ácido acético, ascórbico, bencenosulfónico, benzoico, canfosulfónico, cítrico, etanosulfónico, fumárico, glucónico, glucorónico, glutámico, hipúrico, hidrobrómico, hidroclórico, isetiónico, láctico, lactobiónico, maleico, málico, mandélico, metanosulfónico, múcico, naftalenesulfónico, nicotínico, nítrico, pamoico, pantoténico, fosfórico, succínico, sulfúrico, tartárico, p-toluenosulfónico y otros semejantes.

[0041] También se incluyen sales de aminoácidos, como por ejemplo arginato y otros semejantes y sales de ácidos orgánicos como ácido glucurónico o galactunórico y otros semejantes (ver, por ejemplo, Berge, S. M. et al, "Pharmaceutical Salts", J. Pharmaceutical Science, 1977, 66:1 -19). Ciertos compuestos específicos de la presente invención contienen tanto funcionalidades básicas como acídicas que permiten que los compuestos se

conviertan o bien en sales de adición de base o en sales de adición de ácido.

[0042] Las formas neutras de los compuestos pueden regenerarse poniendo en contacto la sal con una base o ácido y aislando el compuesto parental de la manera convencional. La forma parental del compuesto difieren de las diversas formas de sal en ciertas propiedades físicas, como por ejemplo solubilidad en solventes polares pero de otro modo las sales son equivalentes a la forma parental del compuesto a los fines de la presente invención.

[0043] En el presente contexto, el término “eficaz terapéuticamente” o "cantidad eficaz" indica que los materiales o cantidad de material es eficaz para prevenir, aliviar o mejorar uno o más síntomas de una enfermedad o estado médico y/o prolongar la sobrevivencia del sujeto en tratamiento.

[0044] En el presente contexto, los términos “eficaz sinérgicamente” o “efecto sinérgico” indican que dos o más compuestos que son eficaces terapéuticamente, cuando se usan combinados, proporcionan efectos terapéuticos mejorados superiores a la capacidad de adición que se esperaría con base en el efecto de cada compuesto por separado.

[0045] Se entiende por “probar” la creación de condiciones experimentales y recopilación de datos concernientes a un resultado particular de la exposición a condiciones experimentales específicas. Por ejemplo, se pueden poner a prueba las enzimas

con base en su capacidad de actuar sobre un sustrato detectable. Se puede probar el compuesto en cuando a su capacidad de unirse a una molécula o moléculas meta particulares.

[0046] Según se usan en el presente documento, los términos "ligando" y "modulador" se usan de manera equivalente para referirse a un compuesto que cambia (es decir, aumenta o disminuye) la actividad de una biomolécula meta, *p. ej.,* una enzima, como por ejemplo una quinasa. Por lo general, un ligando o modulador será una molécula pequeña, donde "molécula pequeña" se refiere a un compuesto con un peso molecular de 1500 daltones o menos, o preferiblemente 1000 daltones o menos, 800 daltones o menos, o 600 daltones o menos. Por ende, un "ligando mejorado" es aquel que posee mejores propiedades farmacológicas y/o farmacocinéticas que un compuesto de referencia, donde "mejores" puede significar aquello que la persona capacitada en la tecnología considere para un uso o sistema biológico en particular.

[0047] El término "se une a" en conexión con la interacción que ocurre entre una meta y un compuesto de enlace potencial indica que el compuesto de enlace potencial se vincula con la meta hasta un grado estadísticamente significativo en comparación con la vinculación con proteínas en general (*es decir,* unión no específica). Por ende, el término "compuesto de enlace" se refiere a un compuesto que tiene una asociación estadísticamente significativa con una molécula meta. Preferiblemente un compuesto de enlace interactúa con una meta específica con una constante de

disociación (K_D) de 1 mM o menos, 1 □M o menos, 100 nM o menos, 10 nM o menos, o 1 nM o menos.

[0048] En el contexto de compuestos que se unen a una meta, los términos “mayor afinidad” y "selectivo" indica que el compuesto se une más estrechamente que un compuesto de referencia o que el mismo compuesto en una condición de referencia, *es decir,* con una constante de disociación inferior. En algunas realizaciones, la mayor afinidad es como mínimo 2, 3, 4, 5, 8, 10, 50, 100, 200, 400, 500, 1000, o 10,000 veces mayor.

[0049] Según se usan en el presente documento en conexión con compuestos de la invención, el término “sintetizando” y otros semejantes significa síntesis química de uno o más materiales parentales. Adicionalmente, se entiende por “someter a prueba” la creación de condiciones experimentales y recopilación de datos concernientes a resultados particulares de las condiciones experimentales. Por ejemplo, se pueden probar enzimas con base en su capacidad de actuar sobre un sustrato detectable. Un compuesto o ligando puede probase con base en su capacidad de unirse a una molécula o moléculas meta en particular.

[0050] Según se usan en el presente documento, el término “modulando” o “modular” se refiere al efecto de alterar una actividad biológica, especialmente una actividad biológica vinculada a una biomolécula particular, como por ejemplo, una proteína quinasa. Por ejemplo, un agonista o antagonista de biomolécula particular modula la actividad de esa biomolécula, *p. ej.*,

una enzima, bien sea incrementando (p.ej. agonista, activador), o disminuyendo (p.ej. antagonista, inhibidor) la actividad de la biomolécula, como por ejemplo una enzima. Dicha actividad se indica normalmente en términos de una concentración inhibidora (IC_{50}) o concentración de excitación (EC_{50}) del compuesto para un inhibidor o activador, respectivamente, con respecto a, por ejemplo, una enzima.

[0051] Se entiende por “prodrogas" cualquier compuesto que libera una droga parental activa de conformidad con la Fórmula I *in vivo* cuando dicha prodroga es administrada a un sujeto mamífero. Las prodrogas de un compuesto de fórmula I se preparan modificando grupos funcionales presentes en el compuesto de fórmula I de manera que las modificaciones puedan segmentarse *in vivo* para liberar el compuesto parental. Las prodrogas pueden prepararse mediante la modificación de grupos funcionales presentes en los compuestos de manera que las modificaciones son segmentadas, o bien mediante manipulación de rutina o in vivo, en los compuestos parentales. Las prodrogas incluyen compuestos de fórmula I donde un grupo hidroxi, amino, carboxilo o sulfidrilo en un compuesto de fórmula I se une a cualquier grupo que pueda segmentarse *in vivo* para regenerar el grupo de hidroxilo libre, amino o sulfidrilo, respectivamente. Los ejemplos de prodrogas incluyen, no taxativamente ésteres (*p. ej.*, derivados de acetato, formato y benzoato), amidas, guanidinas, carbamatos (*p. ej.*, N,N-dimetilaminocarbonilo) de grupos hidroxi funcionales en com-

puestos de fórmula I y otros semejantes. La preparación, selección y uso de prodrogas se discute en T. Higuchi y V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 de A.C.S. Symposium Series; "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985; y en Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association y Pergamon Press, 1987, cada uno de los cuales se incorporan en su totalidad al presente documento mediante referencia.

[0052] "Tautómero" significa compuestos producidos mediante el fenómeno donde un protón de un átomo de una molécula cambia a otro átomo. *Ver*, Jerry March, *Advanced Organic Chemistry: Reactions, Mechanisms y Structures*, Fourth Edition, John Wiley & Sons, pages 69-74 (1992). Los tautómeros también se refieren a uno de dos o más isómeros estructurales que existen en equilibrio y se pueden convertir fácilmente de una forma isomérica a otra. Los ejemplos incluyen tautómeros de quetoenol, como por ejemplo acetona/propen-2-ol, tautómeros de imina-enamina y otros semejantes, tautómeros de cadena de anillos, como por ejemplo glucosa/2,3,4,5,6-pentahidroxi-hexanal y otros semejantes, las formas tautoméricas de grupos heteroarilo que contiene un arreglo de átomos de anillos -N=C(H)-NH-, como por ejemplo pirazoles, imidazoles, benzimidazoles, triazoles y tetrazoles. Donde el compuesto contiene, por ejemplo, un grupo queto u oxima o una fracción aromática, puede aparecer un isomerismo tautomérico ('tautomerismo'). Los compuestos descritos en este documento

pueden tener uno o más tautómeros y, en consecuencia, incluyen diversos isómeros. Una persona capacitada en la tecnología sabrá reconocer que son posibles otros arreglos de átomos de anillo tautoméricos. Todas dichas formas isoméricas de estos compuestos están expresamente incluidas en la presente invención.

[0053] "Isómeros" significa compuestos que tienen fórmulas moleculares idénticas pero difieren en su naturaleza o secuencia de unión de sus átomos o en la disposición de sus átomos en el espacio. Los isómeros que difieren en el arreglo de sus átomos en espacio se denominan "estereoisómeros". "Estereoisómero" y "estereoisómeros" se refiere a compuestos que existen en diferentes formas estereoisoméricas si poseen uno o más centros asimétricos o una unión doble con sustitución asimétrica y, en consecuencia, pueden producirse como estereoisómeros individuales o como mezclas. Los estereoisómeros incluyen enantiómeros y diastereómeros. Los etereoisómeros que no son imágenes especulares entre sí se denomina “diastereómeros” y aquellos que son imágenes especulares no sobreponibles se denominan “enantiómeros”. Cuando un compuesto tiene un centro asimétrico, por ejemplo, está unido a cuatro grupos diferentes, es posible un par de enantiomeros. Un enantiómero puede caracterizarse por la configuración absoluta de su centro asimétrico y se describe mediante las normas de secuenciación R- y S-de Cahn y Prelog, o por la manera en la cual la molécula rota el plano de luz polarizada y designada como dextro rotatorio o levo rotatorio (*es decir,* como

isómeros (+) o (−)-respectivamente). Un compuesto quiral puede existir o bien como un enantiómero individual o como una mezcla de los mismos. Una mezcla que contiene proporciones iguales de los enantiómeros se denomina “mezcla racémica”. Salvo que se indique de otro modo, la descripción pretende incluir estereoisómeros individuales así como mezclas. Los métodos para la determinación de estereoquímica y la separación de estereoisómeros son bien conocidos entre la tecnología (*ver* discusión en el Capítulo 4 de ADVANCED ORGANIC CHEMISTRY, 6th edición J. March, John Wiley y Sons, New York, 2007) difieren en cuanto a la quiralidad de uno o más estereocentros.

[0054] Ciertos compuestos de la presente invención pueden existir en formas no solvatadas así como en formas solvatadas, incluyendo formas hidratadas. "Hidrato" se refiere a un complejo formado por una combinación de moléculas de agua con moléculas o iones del soluto. El "solvato" se refiere a un complejo formado por la combinación de moléculas de solvente con moléculas o iones del soluto. El solvente puede ser un compuesto orgánico, un compuesto inorgánico o una mezcla de ambos. Solvato significa que está incluido el hidrato. Algunos ejemplos de solventes incluyen, no taxativamente, metanol, N,N-dimetilformamida, tetrahidrofurano, dimetilsulfóxido y agua. En general, las formas solvatadas son equivalentes a las formas no solvatadas y están abarcadas dentro del alcance de la presente invención. Ciertos compuestos de la presente invención pueden existir en formas

múltiples cristalinas o amorfas. En general, todas las formas físicas son equivalentes para los usos contemplados por la presente invención y se pretende que estén dentro del alcance de la presente invención.

[0055] En el contexto del uso, prueba o tamizado de compuestos que son o pueden ser moduladores, el término "poner en contacto" significa que se hace que el (los) compuesto (s) estén suficientemente cercanos a una molécula, complejo, célula, tejido, organismo en particular u otro material especificado para que puedan ocurrir potenciales interacciones de uniones y/o reacciones químicas entre el compuesto y otro material especificado.

[0056] Según se usan en el presente documento, el término "sujeto" se refiere a un organismo viviente, es decir, tratado con compuestos según se describen en este documento, incluyendo, no taxativamente, cualquier mamífero, como por ejemplo un ser humano, otros primates, animales deportivos, animales de interés comercial como por ejemplo el ganado, animales de granja, como por ejemplo caballos o mascotas, como por ejemplo perros y gatos.

[0057] "Forma sólida" se refiere a una preparación sólida (es decir, una preparación que no es gas ni es líquido) de un compuesto activo farmacéuticamente, es decir adecuado para la administración a un sujeto animal con fines terapéuticos. La forma sólida incluye cualquier complejo, como por ejemplo una sal, co-

cristal o un complejo amorfo, así como cualquier polimorfo del compuesto. La forma sólida puede ser considerablemente cristalina, semicristalina o considerablemente amorfa. La forma sólida puede administrarse directamente o usarse en la preparación de una composición adecuada que tiene propiedades farmacéuticas mejoradas. Por ejemplo, se puede usar la forma sólida en una formulación que comprende como mínimo un soporte o excipiente aceptable farmacéuticamente.

[0058] "Dolor" o "condición de dolor" puede significar un dolor agudo y/o dolor crónico, incluyendo, no taxativamente, aracnoiditis; artritis (p.ej. osteoartritis, artritis reumatoidea, espondilitis anquilosante, gota); dolor de espalda (p.ej. ciática, disco roto, espondilolistesis, radiculopatía); dolor por quemadura; dolor por cáncer; dismenorrea; dolor de cabeza (p.ej. migraña, cefalea histamínica, cefalea tensional); dolor de cabeza y facial (p.ej. neuralgia craneal, neuralgia trigeminal); hiperalgesia; hiperpatía; dolor inflamatorio (p.ej. dolor vinculado con síndrome del colon irritable, enfermedad inflamatoria del colon, colitis ulcerativa, enfermedad de Crohn, cistitis, dolor por infección bacteriana, micótica o viral); formación de queloides o cicatrización; dolor por trabajo de parto o parto; dolor muscular (p.ej. como resultado de polimiositis, dermatomiositis, miositis corporal de inclusión, lesiones provocadas por movimientos repetitivos (p.ej. calambre del escritor, síndrome del túnel carpiano, tendonitis, tenosinovitis));

síndromes de dolor miofascial (p.ej. fibromialgia); dolor neuropático (p.ej. neuropatía diabética, causalgia, neuropatía por atrapamiento, desgarro del plexo braquial, neuralgia occipital, gota, síndrome de distrofia simpática refleja, dolor por miembro fantasma o posterior a amputación, neuralgia posterpética, síndrome de dolor Central o dolor de los nervios como resultado de trauma (p.ej. lesión de los nervios), enfermedades (p.ej. diabetes, esclerosis múltiple, síndrome de Guillan-Barre, miastenia gravis, enfermedades neurodegenerativas como por ejemplo enfermedad de Parkinson, enfermedad de Alzheimer, esclerosis lateral amiotrófica o tratamientos contra el cáncer); dolor vinculado con trastornos de la piel (p.ej. culebrilla, herpes simple, tumores de la piel, quistes, neurofibromatosis); lesiones provocadas por el deporte (p.ej. cortaduras, esguinces, torceduras, hematomas, dislocaciones, fracturas, médula espinal, cabeza); estenosis espinal; dolor quirúrgico; alodinia táctil; trastornos temporomandibular; enfermedad o lesión vascular (p.ej. vasculitis, enfermedad arterial coronaria, lesión por reperfusión (p.ej. posterior a isquemia, accidente cerebro vascular o infartos al miocardio)); dolor en otras órganos o tejidos específicos (p.ej. dolor ocular, dolor de la córnea, dolor de los huesos, dolor Cardiaco, dolor en las vísceras (p.ej. riñón, vesícula, gastrointestinal), dolor de las articulaciones, dolor dental, hipersensibilidad pélvica, dolor pélvico, cólico nefrítico, incontinencia urinaria); otros dolores vinculados a enfermedades

(p.ej. anemia falciforme, SIDA, herpes zoster, soriasis, endometriosis, asma, enfermedad pulmonar obstructiva crónica (COPD), silicosis, sarcoidosis pulmonar, esofagitis, ardor esofágico, trastorno de reflujo gastroesofágico, úlceras estomacales y duodenales, dispepsia funcional, enfermedad de enfermedad de reabsorción ósea, osteoporosis, malaria cerebral, meningitis bacteriana); o dolor debido a rechazo de injerto frente a huésped o rechazo de aloinjertos.

[0059] "Forma de dosis única" se refiere a una composición concebida para una sola administración para trata a un sujeto que padece de un trastorno o condición médica. Cada forma de dosis unitaria comprende normalmente cada uno de los ingredientes activos de esta invención más excipientes aceptables farmacéuticamente. Los ejemplos de formas de dosis unitaria son tabletas individuales, cápsulas individuales, polvos a granel, soluciones liquidas, ungüentos, cremas, gotas oftálmicas, supositorios, emulsiones o suspensiones. El tratamiento de la enfermedad o trastorno puede requerir la administración periódica de formas de dosis unitarias, por ejemplo: una forma de dosis unitaria dos o más veces al día, una con cada comida, una cada cuatro horas u otro intervalo o únicamente una por día. La expresión "forma de dosis unitaria oral" indica una forma de dosis unitaria diseñada para ser tomada oralmente.

[0060] Los compuestos de la presente invención también pueden contener proporciones no naturales de isótopos atómicos en uno o

más de los átomos que constituyen cada compuesto. Por ejemplo, los compuestos pueden ser radio marcados con isótopos radioactivos, como por ejemplo, por ejemplo tritio (^{3}H), yoduro -125 (^{125}I) o carbono -14 (^{14}C). Se pretende que todas las variaciones isotópicas de los compuestos de la presente invención, radioactivos o no, estén comprendidas dentro el alcance de la presente invención.

[0061] Según se usa en el presente documento en conexión con secuencias de aminoácidos o de ácidos nucleicos, el término "aislar" indica que la secuencia se separa de como mínimo una porción de aminoácido y/o ácido nucleico con el cual estaría vinculada normalmente.

[0062] En conexión con secuencias de aminoácidos o ácidos nucleicos, el término "purificado" indica que la molécula objeto constituye una proporción significativamente mayor de las biomoléculas en una composición que la proporción observada en una composición previa, p. ej., en un cultivo celular. La proporción más grande puede ser 2, 5, 10 veces o más de 10 veces con respecto a la proporción hallada en la composición previa.

[0063] La invención también abarca compuestos marcados isotópicamente de la presente invención los cuales son idénticos a los enumerados en el presente documento pero por el hecho de que uno o más átomos son remplazados por un átomo que tiene una masa atómica o número de masa diferente a la masa atómica o número de masa hallado usualmente en la naturaleza. Los ejemplos de isóto-

pos que pueden incorporarse a compuestos de la invención incluyen isótopos de hidrógeno, carbono, nitrógeno, oxigeno, fósforo, flúor y cloro, como por ejemplo, aunque no taxativamente ^{2}H (deuterio, D), ^{3}H (tritio), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P, ^{35}S, ^{36}Cl y ^{125}I. Salvo que se indique de otro modo, cuando una posición es designada específicamente como "H" o "hidrógeno", se entiende que la posición hidrógeno en su composición isotópica o isótopos de abundancia natural, como por ejemplo deuterio (D) o tritio (^{3}H). Ciertos compuestos marcados isotópicamente de la presente invención (p. ej., aquellos marcados con.sup,3H y .sup,14C) son útiles en las pruebas de distribución de compuesto y/o tejido sustrato. Los isótopos tritiados (es decir, ^{3}H) y Carbon-14 (es decir, ^{14}C) son útiles debido a su facilidad de preparación y detectabilidad. Adicionalmente, la sustitución con isótopos más pesados, como por ejemplo deuterio (es decir, ^{2}H) pueden ofrecer ciertas ventajas terapéuticas derivadas de una mayor estabilidad metabólica (p. ej., requisitos de dosis aumentados o reducidos en vida media in vivo) y, por ende, pueden resultar preferidos en ciertas circunstancias. Los compuestos marcados isotópicamente de la presente invención en general pueden prepararse siguiendo procedimientos análogos a los revelados en los esquemas y ejemplos que se presentan más adelante en este documento, sustituyendo un reactivo marcado isotópicamente por un reactivo no marcado isotópicamente.

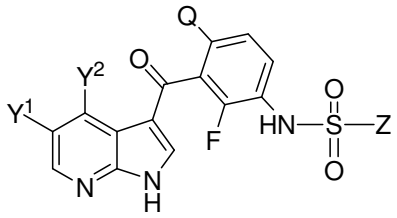
II. General

[0064] La presente invención concierne a compuestos de fórmula I y todas las formulas subgenéricas, compuestos conforme a los enumerados en las reivindicaciones y compuestos descritos en este documento que son moduladores de proteína quinasas, por ejemplo, no taxativamente, los compuestos son moduladores de como mínimo una de las quinasas seleccionadas del grupo que consiste en ABL1, ABL2, ACK, ADRBK1, AKT1, AMPK_A2, A-RAF, ARK5, Aurora_A-C, BMX, CDC42_BPA, CAMK2A, CDK5_p35, CSF1R, DYRK1B, EPHA5, EPHA8, EPHB4, FES, FLT3, FYN, GSK3β, JAK1, KDR, KIT, MAP4K2, MAPK3, MARK2, MARK4, MATK, MET, MINK1, NEK1, NEK2, PAK3, PAK6, PDGFRb, PHKG1, PKC_beta_I, PKC_beta_II, PKC_delta, PKC_gamma, PKC_zeta, SRC, STK24, STK4, ACVR1B_(ALK4), ADRBK2_(GRK3), AKT2_(PKBb), AKT3_(PKBg), ALK, AMPK_A1/B1/G1, ARK5, ASK1, AXL, BRSK1_(SAD1), BrSK2, BTK, CAMK1, CAMK1D, CAMK2A, CAMK2B, CAMK2D, CaMKIdelta, CaMKIIbeta, CaMKIIdelta, CaMKIIgamma, CDC42_BPB, CDK1/CiclinB, CDK2/CiclinA, CDK2/ciclinE, CDK3/ciclinE, CDK5_p25, CDK6/ciclinD3, CDK7/CiclinH/MNAT1, CDK9/CiclinT1, CHEK1, CHEK2, CK1delta, CK1gamma1, CK1gamma2, CK1gamma3, CK2alfa2, CLK1, CLK2, CLK3, CSNK1A1, CSNK1D, CSNK1E, CSNK1G1, CSNK1G2, CSNK1G3, CSNK2A1, CSNK2A2, DAPK1, DAPK2, DAPK3_(ZIPK), DCAMKL2_(DCK2), DDR2, DMPK, DRAK1, DYRK1A, DYRK2, DYRK3, DYRK4, EEF2K, EGFR, EPHA1, EPHA2, EPHA3 EPHA4, EphA7, EPHB1, EPHB2, EPHB3, ERBB2, ERBB4, FER, FGFR1, FGFR2, FGFR3, FGFR4, FLT1, FLT4, FRAP1,GCK, GRK4, GRK5, GRK6, GRK7, GSK3A, GSK3B, Haspin, HCK, activado por hck, HIPK,

HIPK2, HIPK3, HIPK4, IGF1R, activado por IGF-1R, IKBKB, IKBKE, IKKalfa, IKKbeta, INSR, INSRR, activado por IR, IRAK1, IRAK4, ITK, JAK2, JAK2_JH1_JH2, JAK3, JNK1alfa1, JNK2alfa2, activado por Lck, LIMK1, LKB1, LOK, LTK, MAP2K1, MAP2K2, MAP2K6, MAP3K8, MAP3K9, MAP4K4, MAPK1, MAPK10, MAPK11, MAPK12, MAPK13, MAPK14, MAPK2, MAPK8, MAPK9, MAPKAPK2, MAPKAPK3, MAPKAPK5, MARK1, MARK3, MELK, MERTK, MKK7beta, MLCK, MRCKalfa, MRCKbeta, MST1R, MST4, mTOR/FKBP12, MUSK, NEK3, NEK4, NEK6, NEK7, NEK9, NLK, NTRK1, NTRK2, NTRK3, PAK2, PAK4, PAK7_(KIAA1264), PAR-1Balfa, PASK, PDGFRalfa, PDGFRbeta, PDK1, PHKG2, PhKgamma2, PIK3CA/PIK3R1, PIK3CG,) PIM1, PIM2, Pim-3, PKBalfa, PKBbeta, PKBgamma, PKCalfa, PKCbetaI, PKCbetaII, PKCdelta, PKCepsilon, PKCeta, PKCgamma, PKCiota, PKCmu, PKCtheta, PKCzeta, PKG1alfa, PKG1beta, PKN1, PLK2, PLK3, PRK2, PRKACA, PRKCA, PRKCE, PRKCH, PRKCI, PRKCN, PRKCQ, PRKD1, PRKD2, PRKG1, PRKG2, PRKX, PTK2, PTK2B, RET, RIPK2, ROCK1, ROCK2, ROS1, RPS6KA1, RPS6KA2, RPS6KA3, RPS6KA4, RPS6KA5, RPS6KA6, RPS6KB1, SGK, SGK2, SGKL, SIK, SNF1LK2, Snk, SRPK1, SRPK2, STK22B, STK22D, STK23, STK25, STK3, STK33, SYK, TAK1, TAO3, TAOK2, TBK1, activado por Tec, TEK, TLK2, Txk, TYK2, TYRO3, ULK2, ULK3, VRK2, WNK2, WNK3 y ZAP70 y el uso de dichos compuestos en el tratamiento de enfermedades o condiciones. En algunas realizaciones, las quinasas tienen menos de 20% de inhibición en 1 µM. En otras realizaciones, las quinasas tienen menos de 10% de inhibición en 1 µM.

III. Compuestos

[0065] En un aspecto, la presente invención proporciona compuestos de fórmula (I):



I

y sales, hidratos, solvatos, tautómeros e isómeros aceptables farmacéuticamente; donde los sustituyentes han sido definidos en el resumen de la invención.

[0066] En algunas realizaciones de compuestos de fórmula (I) y^1 ha sido definido en el resumen de la invención. Todos los demás sustituyentes de fórmula (I) han sido definidos en cualquiera de las realizaciones descritas en este documento. En algunas realizaciones preferidas, los compuestos tienen pesos moleculares inferiores a 600, más preferiblemente, los compuestos tienen pesos moleculares inferiores a 550. En otras realizaciones preferidas, los compuestos tienen pesos moleculares inferiores a 500.

[0067] En algunas realizaciones de compuestos de fórmula (I) y^1 es CN, halógeno, -OH, C_{1-6} alquilo, C_{1-6} alcoxi, C_{3-6}cicloalquilo, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, arilo o heteroarilo, donde la porción alifática o aromática de Y^1 es cada una por separado sustituida opcionalmente con 1-5 R^1 sustituyentes; cada R^1 es seleccionado por separado de C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, C_{3-8} cicloalquilo, C_{3-8} cicloal-

quilo-C_{1-4}-alquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, heterocicloalquilo, heterocicloalquilo-C_{1-4} alquilo o $-R^a$, donde R^a es seleccionado de halógeno, $-CH=CH_2$, $-CN$, $-OH$, $-NH_2$, $-NO_2$, $-C(O)OH$, $-C(S)OH$, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^b$, $-SR^b$, $-OC(O)R^b$, $-OC(S)R^b$, $-C(O)R^b$, $-C(S)R^b$, $-C(O)OR^b$, $-C(S)OR^b$, $-S(O)R^b$, $-S(O)_2R^b$, $-C(O)NHR^b$, $-C(S)NHR^b$, $-C(O)NR^bR^b$, $-C(S)NR^bR^b$, $-S(O)_2NHR^b$, $-S(O)_2NR^bR^b$, $-C(NH)NHR^b$, $-C(NH)NR^bR^b$, $-NHC(O)R^b$, $-NHC(S)R^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NHS(O)_2R^b$, $-NR^bS(O)_2R^b$, $-NHC(O)NHR^b$, $-NHC(S)NHR^b$, $-NR^bC(O)NH_2$, $-NR^bC(S)NH_2$, $-NR^bC(O)NHR^b$, $-NR^bC(S)NHR^b$, $-NHC(O)NR^bR^b$, $-NHC(S)NR^bR^b$, $-NR^bC(O)NR^bR^b$, $-NR^bC(S)NR^bR^b$, $-NHS(O)_2NHR^b$, $-NR^bS(O)_2NH_2$, $-NR^bS(O)_2NHR^b$, $-NHS(O)_2NR^bR^b$, $-NR^bS(O)_2NR^bR^b$, $-NHR^b$ o $-NR^bR^b$, donde cada R^b es seleccionado por separado del grupo que consiste en C_{1-6}alquilo, halógeno, $-CN$, C_{1-6}alcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquilo-C_{1-4}-alquilo, $-OH$, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, arilo, arilo-C_{1-4}alquilo, heteroarilo y heteroariloalquilo; o dos R^b sustituyentes cuando están unidos al mismo átomo de nitrógeno tomados junto con el átomo de nitrógeno forman un anillo de tres a ocho miembros que tiene de 0-2 heteroátomos adicionales como miembros de anillo seleccionados de N, O o S; donde la porción alifática o aromática de R^1 es sustituida opcionalmente además con 1-3 grupos seleccionados de C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, heterocicloalquilo, heterocicloalquilo-C_{1-4}alquilo o $-R^c$, donde cada R^c es seleccio-

nado por separado de halógeno, $-CH=CH_2$, $-CN$, $-OH$, $-NH_2$, $-NO_2$, $-C(O)OH$, $-C(S)OH$, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^d$, $-SR^d$, $-OC(O)R^d$, $-OC(S)R^d$, $-C(O)R^d$, $-C(S)R^d$, $-C(O)OR^d$, $-C(S)OR^d$, $-S(O)R^d$, $-S(O)_2R^d$, $-C(O)NHR^d$, $-C(S)NHR^d$, $-C(O)NR^dR^d$, $-C(S)NR^dR^d$, $-S(O)_2NHR^d$, $-S(O)_2NR^dR^d$, $-C(NH)NHR^d$, $-C(NH)NR^dR^d$, $-NHC(O)R^d$, $-NHC(S)R^d$, $-NR^dC(O)R^d$, $-NR^dC(S)R^d$, $-NHS(O)_2R^d$, $-NR^dS(O)_2R^d$, $-NHC(O)NHR^d$, $-NHC(S)NHR^d$, $-NR^dC(O)NH_2$, $-NR^dC(S)NH_2$, $-NR^dC(O)NHR^d$, $-NR^dC(S)NHR^d$, $-NHC(O)NR^dR^d$, $-NHC(S)NR^dR^d$, $-NR^dC(O)NR^dR^d$, $-NR^dC(S)NR^dR^d$, $-NHS(O)_2NHR^d$, $-NR^dS(O)_2NH_2$, $-NR^dS(O)_2NHR^d$, $-NHS(O)_2NR^dR^d$, $-NR^dS(O)_2NR^dR^d$, $-NHR^d$, R^f o $-NR^dR^d$, donde cada R^d es seleccionado por separado de C_{1-6} alquilo, ariloalquilo, arilo, heteroarilo, heteroariloalquilo, cicloalquilo, cicloalquiloalquilo, heterocicloalquilo o heterocicloalquiloalquilo; y donde la porción aromática de R^1 es sustituida opcionalmente con 1-3 sustituyentes seleccionados por separado de R^e, donde R^e se selecciona del grupo que consiste en halógeno, $-CH=CH_2$, $-CN$, $-OH$, $-NH_2$, $-NO_2$, $-C(O)OH$, $-C(S)OH$, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^f$, $-SR^f$, $-OC(O)R^f$, $-OC(S)R^f$, $-C(O)R^f$, $-C(S)R^f$, $-C(O)OR^f$, $-C(S)OR^f$, $-S(O)R^f$, $-S(O)_2R^f$, $-C(O)NHR^f$, $-C(S)NHR^f$, $-C(O)NR^fR^f$, $-C(S)NR^fR^f$, $-S(O)_2NHR^f$, $-S(O)_2NR^fR^f$, $-C(NH)NHR^f$, $-C(NH)NR^fR^f$, $-NHC(O)R^f$, $-NHC(S)R^f$, $-NR^fC(O)R^f$, $-NR^fC(S)R^f$, $-NHS(O)_2R^f$, $-NR^fS(O)_2R^f$, $-NHC(O)NHR^f$, $-NHC(S)NHR^f$, $-NR^fC(O)NH_2$, $-NR^fC(S)NH_2$, $-NR^fC(O)NHR^f$, $-NR^fC(S)NHR^f$, $-NHC(O)NR^fR^f$, $-NHC(S)NR^fR^f$, $-NR^fC(O)NR^fR^f$, $-NR^fC(S)NR^fR^f$, $-NHS(O)_2NHR^f$, $-NR^fS(O)_2NH_2$,

$-NR^fS(O)_2NHR^f$, $-NHS(O)_2NR^fR^f$, $-NR^fS(O)_2NR^fR^f$, $-NHR^f$, $-NR^fR^f$ y R^f, donde R^f es C_{1-6}alquilo o arilo; o dos grupos adyacentes R^1 en el anillo de arilo o heteroarilo junto con los átomos a los cuales están unidos forman un anillo de 5 o 6 miembros que tiene de 0 a 2 heteroátomos adicionales seleccionados de N, O o S, sustituido opcionalmente con 1 a 3 R^d o R^e sustituyentes. En algunos casos, R^f es C_{1-6}alquilo. En otros casos, R^f es arilo, como por ejemplo fenilo. Todas las otras variables Y^2, Q, Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidos en cualquiera de las realizaciones descritas en este documento.

[0068] En algunas realizaciones de compuestos de fórmula (I) y^1 es arilo o grupos heteroarilo, donde el grupo heteroarilo tiene de 1 a 4 heteroátomos como miembros de anillo seleccionados de N, O o S; y donde e arilo o grupos heteroarilo son sustituidos opcionalmente con 1 a 3 R^1 sustituyentes; o dos grupos adyacentes R^1 en el anillo de fenilo o naftilo junto con los átomos a los cuales están unidos forman un anillo de 5 o 6 miembros que tiene de 0 a 2 heteroátomos adicionales seleccionados de N, O o S, sustituido opcionalmente con 1 a 3 R^d sustituyentes. En otras realizaciones y^1 es CN, halógeno, -OH, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6}haloalquilo o C_{1-6}haloalcoxi. En algunos casos y^1 es fenilo, 1-naftilo o 2-naftilo, cada uno de los cuales es sustituido opcionalmente con uno a tres R^1. En otros casos y^1 es fenilo, 1-naftilo o 2-naftilo, cada uno de los cuales es sustituido opcionalmente con uno a tres R^a. En otros casos y^1 es fenilo, 1-

naftilo o 2-naftilo, cada uno de los cuales es sustituido opcionalmente con uno a tres R^b. En otros casos y^1 es fenilo, 1-naftilo o 2-naftilo, cada uno de los cuales es sustituido opcionalmente con uno a tres R^c. En otros casos y^1 es fenilo, 1-naftilo o 2-naftilo, cada uno de los cuales es sustituido opcionalmente con uno a tres R^d. En otros casos y^1 es fenilo, 1-naftilo o 2-naftilo, cada uno de los cuales es sustituido opcionalmente con uno a tres R^e. En otros casos y^1 es fenilo, 1-naftilo o 2-naftilo, cada uno de los cuales es sustituido opcionalmente con uno a tres R^a. En algunos casos y^1 es fenilo, 1-naftilo o 2-naftilo, es F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O–, CH_3–, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo o metilcarbamoilo. Todas las otras variables Y^2, Q, Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0069] En algunas realizaciones de compuestos de fórmula (I) y^1 es 1H-4-benzotriazolilo, 1H-5-benzotriazolilo, 1H-4-benzimidazolilo, 1H-5-benzimidazolilo, 1H-4-indazolilo, 1H-5-indazolilo, 1H-6-indazolilo, 1H-7-indazolilo, 1H-4-indolilo, 1H-5-indolilo, 1H-6-indolilo, 1H-7-indolilo, 2-oxo-6-indolinilo, 2-oxo-4-indolinilo, 2-oxo-5-indolinilo, 2-oxo-7-indolinilo, 1,2-

benzoxazol-4-il, 1,2-benzoxazol-5-il, 1,2-benzoxazol-6-il, 1,2-benzoxazol-7-il, 1,3-benzoxazol-4-il, 1,3-benzoxazol-5-il, 1,3-benzoxazol-6-il, 1,3-benzoxazol-7-il, 1,2-benzotiazol-4-il, 1,2-benzotiazol-5-il, 1,2-benzotiazol-6-il, 1,2-benzotiazol-7-il, 5-quinolinilo, 6-quinolinilo, 7-quinolinilo, 8-quinolinilo, 5-isoquinolinilo, 6-isoquinolinilo, 7-isoquinolinilo, 8-isoquinolinilo, 5-cinnolinilo, 6-cinnolinilo, 7-cinnolinilo, 8-cinnolinilo, 5-quinazolinilo, 6-quinazolinilo, 7-quinazolinilo, 8-quinazolinilo, 5-quinoxalinilo, 6-quinoxalinilo, 7-quinoxalinilo, 8-quinoxalinilo, 4-indanilo, 5-indanilo, 5-tetralinilo, 6-tetralinilo, 1,3-dihidroisobenzofuran-4-ilo, 1,3-dihidroisobenzofuran-5-ilo, 2,3-dihidrobenzofuran-4-ilo, 2,3-dihidrobenzofuran-5-ilo, 2,3-dihidrobenzofuran-6-ilo, 2,3-dihidrobenzofuran-7-ilo, 1,3-dihidroisobenzotiofen-4-ilo, 1,3-dihidroisobenzotiofen-5-ilo, 2,3-dihidrobenzotiofen-4-ilo, 2,3-dihidrobenzotiofen-5-ilo, 2,3-dihidrobenzotiofen-6-ilo, 2,3-dihidrobenzotiofen-7-ilo, 4-indolinilo, 5-indolinilo, 6-indolinilo, 7-indolinilo, 5-isocromanilo, 6-isocromanilo, 7-isocromanilo, 8-isocromanilo, 5-cromanilo, 6-cromanilo, 7-cromanil, 8-cromanilo, 2,3-dihidro-1,3-benzotiazo-4-ilo, 2,3-dihidro-1,3-benzotiazo-5-ilo, 2,3-dihidro-1,3-benzotiazo-6-ilo, 2,3-dihidro-1,3-benzotiazo-7-ilo, 2,3-dihidro-1,2-benzotiazo-4-ilo, 2,3-dihidro-1,2-benzotiazo-5-ilo, 2,3-dihidro-1,2-benzotiazo-6-ilo, 2,3-dihidro-1,2-benzotiazo-7-ilo, 2,3-dihidro-1,3-benzoxazol-4-ilo, 2,3-dihidro-1,3-benzoxazol-5-ilo, 2,3-

dihidro-1,3-benzoxazol-6-ilo, 2,3-dihidro-1,3-benzoxazol-7-iol, 2,3-dihidro-1,2-benzoxazol-4-ilo, 2,3-dihidro-1,2-benzoxazol-5-ilo, 2,3-dihidro-1,2-benzoxazol-6-ilo, 2,3-dihidro-1,2-benzoxazol-7-ilo, 4-benzofuranilo, 5-benzofuranilo, 6-benzofuranilo, 7-benzofuranilo, 4-benzotiofenilo, 5-benzotiofenilo, 6-benzotiofenilo o 7-benzotiofenilo, cada uno de los cuales es sustituido opcionalmente con 1 a 3 R^1 sustituyentes; o 1 a 3 R^a sustituyentes; o 1 a 3 R^b sustituyentes; o 1 a 3 R^c sustituyentes; o 1 a 3 R^d sustituyentes; o 1 a 3 R^e sustituyentes; 1 a 3 R^f sustituyentes; o 1 a 3 sustituyentes seleccionados de F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo o metilcarbamoilo. Todas las otras variables Y^2, Q, Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0070] En algunas realizaciones y^1 es heteroarilo de 5 o 6 miembros, cada uno de los cuales se sustituye opcionalmente por separado con 1-3 R^1 grupos, donde la porción aromática de R^1 es sustituida opcionalmente con 1-3 sustituyentes seleccionados por separado de R^e; o dos grupos adyacentes R^1 en el anillo de fenilo o naftilo junto con los átomos a los cuales están unidos forman

un anillo de 5 o 6 miembros que tiene de 0 a 2 heteroátomos adicionales seleccionados de N, O o S, sustituido opcionalmente con 1 a 3 R^d sustituyentes. Todas las otras variables Y^2, Q, Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0071] En algunas realizaciones de compuestos de fórmula (I) y^1 es 5-pirimidinilo, 2-pirimidinilo, 4-pirimidinilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-piracinilo, 2-piridacinilo, 3-piridacinilo, 1-pirrolilo, 2-pirrolilo, 3-pirrolilo, 2-imidazolilo, 4-imidazolilo, 1-pirazolilo, 2-pirazolilo, 3-pirazolilo, 2-oxazolilo, 4-oxazolilo, 5-oxazolilo, 2-tiazolilo, 4-tiazolilo, 5-tiazolilo, 3-isoxazolilo, 4-isoxazolilo, 5-isoxazolilo, 3-isotiazolilo, 4-isotiazolilo, 5-isotiazolilo, 1,2,3-triazol-1-il, 1,2,3-triazol-2-il, 1,2,3-triazol-3-il, 1,2,3-triazol-4-il, 1,2,3-triazol-5-il, 1,2,4-triazol-1-il, 1,2,4-triazol-2-il, 1,2,4-triazol-3-il, 1,2,4-triazol-4-il, 1,2,4-triazol-5-il, 1-oxa-2,3-diazol-4-il, 1-oxa-2,3-diazol-5-il, 1-oxa-2,4-diazol-3-il, 1-oxa-2,4-diazol-5-il, 1-oxa-2,5-diazol-3-il, 1-oxa-2,5-diazol-4-il, 1-tia-2,3-diazol-4-il, 1-tia-2,3-diazol-5-il, 1-tia-2,4-diazol-3-il, 1-tia-2,4-diazol-5-il, 1-tia-2,5-diazol-3-il, 1-tia-2,5-diazol-4-il, 1-tetrazolilo, 3-tetrazolilo, 1H-5-tetrazolilo, 3H-5-tetrazolilo, 2-furanilo, 3-furanilo, 2-tiopenil o 3-tiofenilo, cada uno de los cuales es sustituido opcionalmente con 1 a 3 sustituyentes R^1; o 1 a 3 sustituyentes R^a; o 1 a 3 sustituyentes R^b; o 1 a 3 sustituyentes

R^c; o 1 a 3 sustituyentes R^d; o 1 a 3 sustituyentes R^e; 1 a 3 sustituyentes R^f; o 1 a 3 sustituyentes seleccionados de F, Cl, Br, I, –CN, –OH, $–CF_3$, NH_2, $CF_3O–$, $CH_3–$, CH_3O, $–NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1–cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, 1–ciclopropiloetilo, 2–ciclopropiloetilo, 1–ciclopropiloetilamino, 2–ciclopropiloetilamino, 1–hidroxi–1–metiletilo, metilcarbamoilo, 1–carboxiciclopropilo, 1–carbamoilociclopropilo, 1–metoxicarbonilociclopropilo, 1–cianoisopropilo, 1–hidroxiciclopropilo, 1–hidroxiisopropilo, ciclobutoxi, ciclopentoxi, cicloheiloxi, 4–morfolino, 4–hidroxipiperidinilo,1– piperidinilo, piperacinilo, 4–metilpiperacinilo, 4–t–butoxicarbonilopiperacinilo, azetidinilo, pirrolidinilo, ciclopropilocarbamoilo, 5–metil–1,2,4–oxadiazol–3–il, 5–metil–1,3,4–oxadiazol–2ilo, 5–dimetilamino–1,3,4–oxadiazol–2ilo o 5–metilamino–1,3,4–tiadiazol–2–ilo. Todas las otras variables Y^2, Q, Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0072] En ciertas realizaciones de compuestos de fórmula (I) y^1 se selecciona del grupo que consiste en 4–pirimidinilo, 5–pirimidinilo, 2–piracinilo, 2–tiazolilo, 4–tiazolilo, 5–tiazolilo, 2– tiofenilo, 3–tiofenilo, 2–amino–quinazolin–5–ilo, 2–amino–quinazolin–6–ilo, 2–amino–quinazolin–6–il, 2–amino–quinazolin–7–ilo, 2–amino–quinazolin–8–ilo, 2–oxo–6–indolinilo,

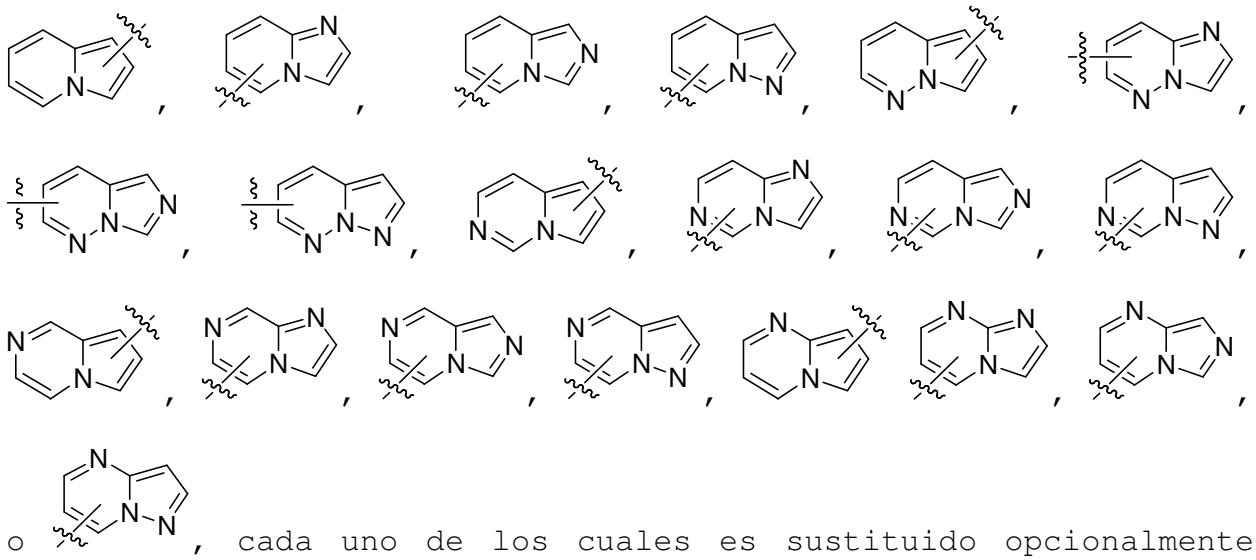
2-oxo-4-indolinilo, 2-oxo-5-indolinilo, 2-oxo-7-indolinilo, 2-piridilo, 3-piridilo, 4-piridilo, 1H-indazol-4-ilo, 1H-indazol-5-ilo, 1H-indazol-6-ilo y 1H-indazol-7-ilo, cada uno de los cuales es sustituido con 1 a 2 sustituyentes seleccionados por separado de F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, C_2H_5O-, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, 1-carboxiciclopropilo, 1-carbamoilociclopropilo, 1-metoxicarbonilociclopropilo, 1-cianoisopropilo, 1-hidroxiciclopropilo, 1-hidroxiisopropilo, ciclobutoxi, ciclopentoxi, cicloheiloxi, 4-morfolino, 4-hidroxipiperidinilo,1- piperidinilo, piperacinilo, 4-metilpiperacinilo, 4-t-butoxicarbonilopiperacinilo, azetidinilo, pirrolidinilo, ciclopropilocarbamoilo, 5-metil-1,2,4-oxadiazol-3-ilo, 5-metil-1,3,4-oxadiazol-2ilo, 5-dimetilamino-1,3,4-oxadiazol-2il, 5-metilamino-1,3,4-tiadiazol-2-ilo, metilamino metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, isopropilo, 1-pirrolidinilo, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo. Todas las otras variables Y^2, Q, Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0073] En otras realizaciones de compuestos de fórmula (I) y^1 es 1-benzotriazolilo, 1-benzimidazolilo, 1H-2-benzimidazolilo,

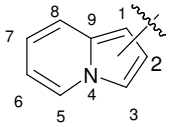
1-indazolilo, 1H-3-indazolilo, 1-indolilo, 1H-2-indolilo, 1H-3-indolilo, 1,2-benzoxazol-3-ilo, 1,3-benzoxazol-2-ilo, 1,2-benzotiazol-3-ilo, 1,3-benzotiazol-2-ilo, 2-quinolinilo, 3-quinolinilo, 4-quinolinilo, 1-isoquinolinilo, 3-isoquinolinilo, 4-isoquinolinilo, 3-cinnolinilo, 4-cinnolinilo, 2-quinazolinilo, 4-quinazolinilo, 2-quinoxalinilo, 2-benzofuranilo, 3-benzofuranilo, 2-benzotiofenilo o 3-benzotiofenilo, cada uno de los cuales es sustituido opcionalmente con 1 a 3 sustituyentes R^1; o 1 a 3 R^a sustituyentes; o 1 a 3 sustituyentes R^b; o 1 a 3 sustituyentes R^c; o 1 a 3 sustituyentes R^d; o 1 a 3 sustituyentes R^e; 1 a 3 sustituyentes R^f; o 1 a 3 sustituyentes seleccionados de F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O–, CH_3–, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino, 1-hidroxi-1-metiletilo, metilcarbamoilo, 1-carboxiciclopropilo, 1-carbamoilociclopropilo, 1-metoxicarbonilociclopropilo, 1-cianoisopropilo, 1-hidroxiciclopropilo, 1-hidroxiisopropilo, ciclobutoxi, ciclopentoxi, cicloheiloxi, 4-morfolino, 4-hidroxipiperidinilo,1- piperidinilo, piperacinilo, 4-metilpiperacinilo, 4-t-butoxicarbonilopiperacinilo, azetidinilo, pirrolidinilo, ciclopropilocarbamoilo, 5-metil-1,2,4-oxadiazol-3-ilo, 5-metil-1,3,4-oxadiazol-2ilo, 5-dimetilamino-1,3,4-oxadiazol-2ilo o 5-

metilamino-1,3,4-tiadiazol-2-ilo. Todas las otras variables Y^2, Q, Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

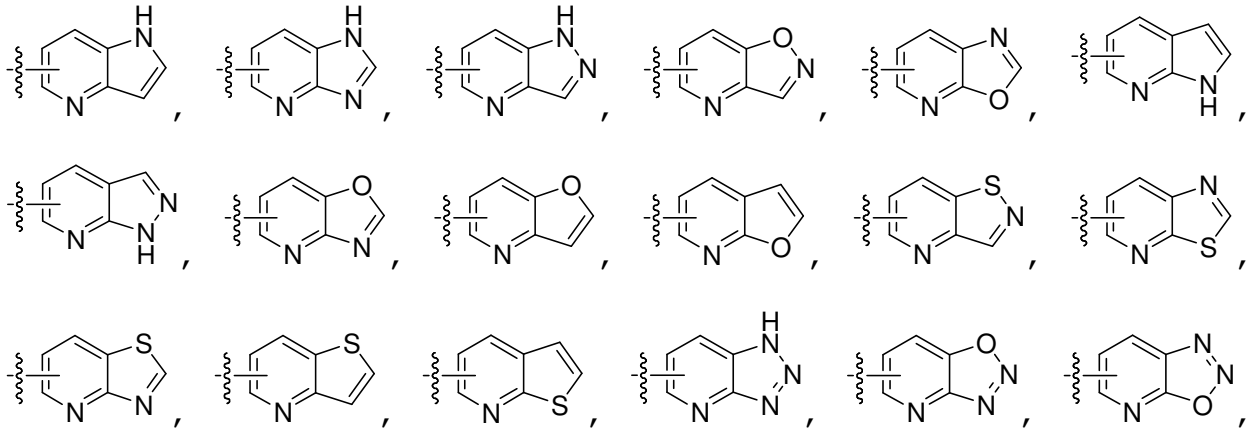
[0074] En algunas realizaciones de compuestos de fórmula (I) y^1 es seleccionado de:

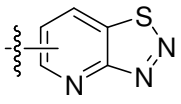
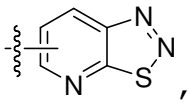


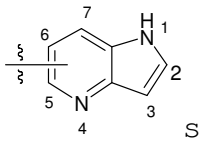
, cada uno de los cuales es sustituido opcionalmente con 1 a 3 sustituyentes R^1; o 1 a 3 sustituyentes R^a; o 1 a 3 sustituyentes R^b; o 1 a 3 R^c sustituyentes; o 1 a 3 R^d sustituyentes; o 1 a 3 R^e sustituyentes; 1 a 3 R^f sustituyentes; o 1 a 3 sustituyentes seleccionados de F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino, 1-hidroxi-1-metiletilo, metilcarbamoilo, 1-carboxiciclopropilo, 1-carbamoilociclopropilo, 1-metoxicarbonilociclopropilo, 1-cianoisopropilo, 1-hidroxiciclopropilo, 1-hidroxiisopropilo, ci-

clobutoxi, ciclopentoxi, cicloheiloxi, 4-morfolino, 4-hidroxipiperidinilo,1- piperidinilo, piperacinilo, 4-metilpiperacinilo, 4-t-butoxicarbonilopiperacinilo, azetidinilo, pirrolidinilo, ciclopropilocarbamoilo, 5-metil-1,2,4-oxadiazol-3-il, 5-metil-1,3,4-oxadiazol-2ilo, 5-dimetilamino-1,3,4-oxadiazol-2ilo o 5-metilamino-1,3,4-tiadiazol-2-ilo, donde la línea ondulada indica el punto de unión al resto de la molécula. La notación —§- significa que Y^1 puede estar unido al resto de la molécula en cualquiera de las posiciones disponibles del grupo Y^1 establecido anteriormente. Por ejemplo,  significa que está incluido 1-indolicinilo, 2-indolicinilo, 3-indolicinilo, 4-indolicinilo, 5-indolicinilo, 6-indolicinilo, 7-indolicinilo y 8-indolicinilo (es decir, las sustituciones pueden ser en las posiciones 1, 2, 3, 5, 6, 7 u 8 del anillo de indolizina).

[0075] En algunas realizaciones de compuestos de fórmula (I) y^1 es seleccionado de:

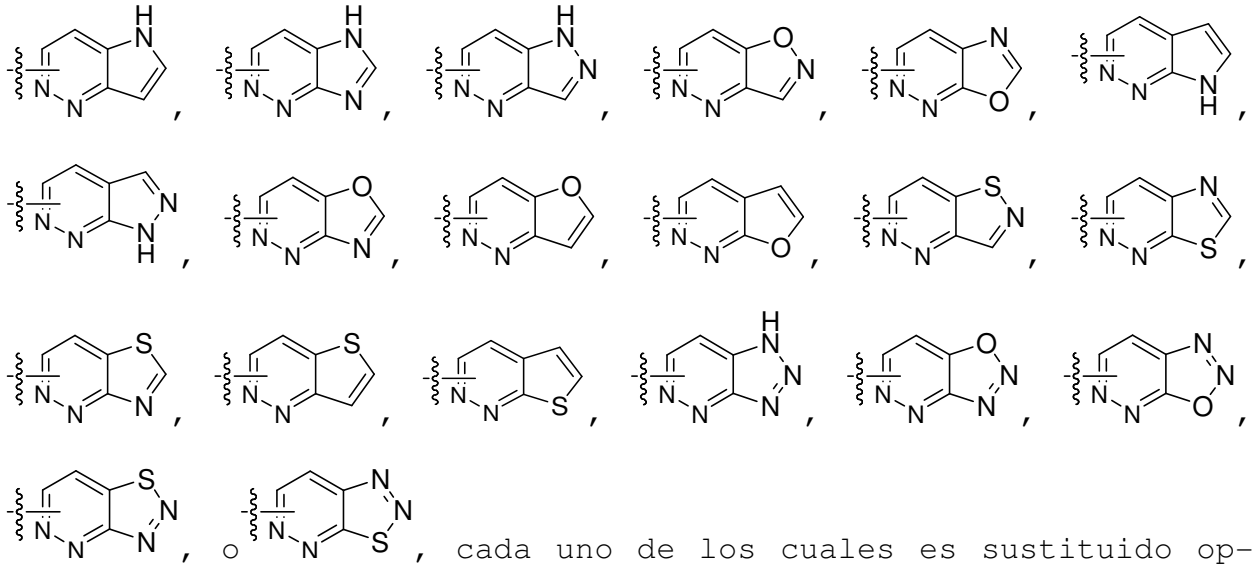


 o  , cada uno de los cuales es sustituido opcionalmente con 1 a 3 R^1 sustituyentes; o 1 a 3 sustituyentes R^a; o 1 a 3 sustituyentes R^b; o 1 a 3 sustituyentes R^c; o 1 a 3 sustituyentes R^d; o 1 a 3 sustituyentes R^e; 1 a 3 sustituyentes R^f; o 1 a 3 sustituyentes seleccionados de F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1–cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, 1–ciclopropiloetilo, 2–ciclopropiloetilo, 1–ciclopropiloetilamino, 2–ciclopropiloetilamino, 1–hidroxi–1–metiletilo, metilcarbamoilo, 1–carboxiciclopropilo, 1–carbamoilociclopropilo, 1–metoxicarbonilociclopropilo, 1–cianoisopropilo, 1–hidroxiciclopropilo, 1–hidroxiisopropilo, ciclobutoxi, ciclopentoxi, cicloheiloxi, 4–morfolino, 4–hidroxipiperidinilo,1– piperidinilo, piperacinilo, 4–metilpiperacinilo, 4–t–butoxicarbonilopiperacinilo, azetidinilo, pirrolidinilo, ciclopropilocarbamoilo, 5–metil–1,2,4–oxadiazol–3–ilo, 5–metil–1,3,4–oxadiazol–2il, 5–dimetilamino–1,3,4–oxadiazol–2ilo o 5–metilamino–1,3,4–tiadiazol–2–ilo, donde la línea ondulada indica el punto de unión al resto de la molécula. La notación significa que Y^1 puede estar unido al resto de la molécula en cualquiera de las posiciones disponibles del grupo Y^1 establecido an–

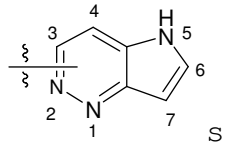


teriormente. Por ejemplo, significa que está incluido 1H-pirrolo[3,2-b]piridin-1-il, 1H-pirrolo[3,2-b]piridin-2-il, 1H-pirrolo[3,2-b]piridin-3-il, 1H-pirrolo[3,2-b]piridin-5-il, 1H-pirrolo[3,2-b]piridin-6-il y 1H-pirrolo[3,2-b]piridin-7-il (es decir, las sustituciones pueden ser en las posiciones 1, 2, 3, 5, 6, o 7 del anillo pirrolo[3,2-b]piridina). Todas las otras variables Y^2, Q, Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0076] En algunas realizaciones de compuestos de fórmula (I) y^1 es seleccionado de:

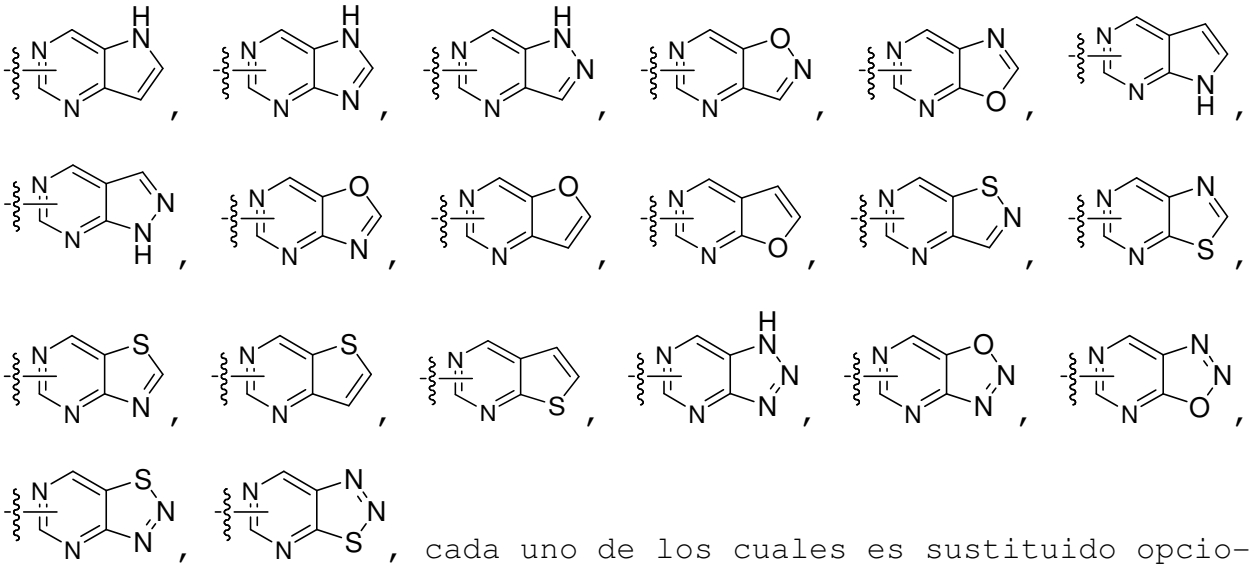


, cada uno de los cuales es sustituido opcionalmente con 1 a 3 sustituyentes R^1; o 1 a 3 sustituyentes R^a; o 1 a 3 sustituyentes R^b; o 1 a 3 sustituyentes R^c; o 1 a 3 sustituyentes R^d; o 1 a 3 sustituyentes R^e; 1 a 3 sustituyentes R^f; o 1 a 3 sustituyentes seleccionados de F, Cl, Br, I, –CN, –OH, –

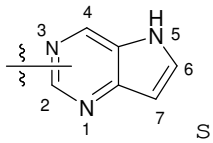
CF_3, NH_2, CF_3O–, CH_3–, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino, 1-hidroxi-1-metiletilo, metilcarbamoilo, 1-carboxiciclopropilo, 1-carbamoilociclopropilo, 1-metoxicarbonilociclopropilo, 1-cianoisopropilo, 1-hidroxiciclopropilo, 1-hidroxiisopropilo, ciclobutoxi, ciclopentoxi, cicloheiloxi, 4-morfolino, 4-hidroxipiperidinilo,1- piperidinilo, piperacinilo, 4-metilpiperacinilo, 4-t-butoxicarbonilopiperacinilo, azetidinilo, pirrolidinilo, ciclopropilocarbamoilo, 5-metil-1,2,4-oxadiazol-3-ilo, 5-metil-1,3,4-oxadiazol-2il, 5-dimetilamino-1,3,4-oxadiazol-2ilo o 5-metilamino-1,3,4-tiadiazol-2-ilo, donde la línea ondulada indica el punto de unión al resto de la molécula. La notación  significa que Y^1 puede estar unido al resto de la molécula en cualquiera de las posiciones disponibles del grupo Y^1 establecido anteriormente. Por ejemplo,  significa que está incluido 5H-pirrolo[3,2-c]piridazin-3-ilo, 5H-pirrolo[3,2-c]piridazin-4-ilo, 5H-pirrolo[3,2-c]piridazin-5-ilo, 5H-pirrolo[3,2-c]piridazin-6-ilo, 5H-pirrolo[3,2-c]piridazin-7-ilo (es decir, las sustituciones pueden ser en las posiciones 3, 4, 5, 6, o 7

del anillo de 5H-pirrolo[3,2-c]piridazina). Todas las otras variables Y^2, Q, Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

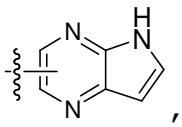
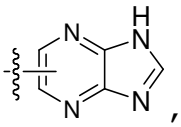
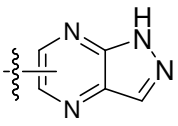
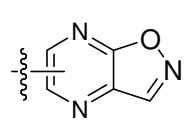
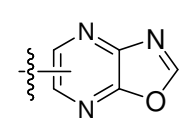
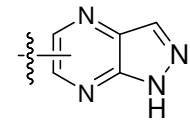
[0077] En algunas realizaciones de compuestos de fórmula (I) y^1 es seleccionado de:

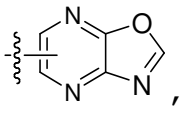
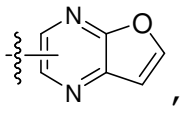
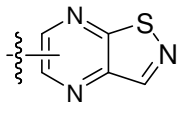
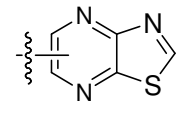
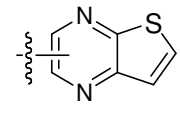
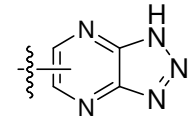


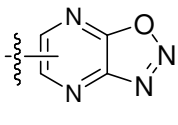
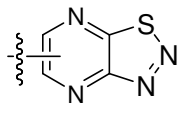
, cada uno de los cuales es sustituido opcionalmente con 1 a 3 sustituyentes R^1; o 1 a 3 sustituyentes R^a; o 1 a 3 sustituyentes R^b; o 1 a 3 sustituyentes R^c; o 1 a 3 sustituyentes R^d ; o 1 a 3 sustituyentes R^e; 1 a 3 sustituyentes R^f; o 1 a 3 sustituyentes seleccionados de F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino, 1-hidroxi-1-metiletilo, metilcarbamoilo, 1-carboxiciclopropilo, 1-carbamoilociclopropilo, 1-

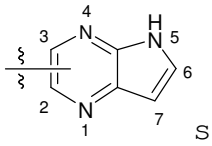
metoxicarbonilociclopropilo, 1-cianoisopropilo, 1-hidroxiciclopropilo, 1-hidroxiisopropilo, ciclobutoxi, ciclopentoxi, cicloheiloxi, 4-morfolino, 4-hidroxipiperidinilo,1- piperidinilo, piperacinilo, 4-metilpiperacinilo, 4-t-butoxicarbonilopiperacinilo, azetidinilo, pirrolidinilo, ciclopropilocarbamoilo, 5-metil-1,2,4-oxadiazol-3-ilo, 5-metil-1,3,4-oxadiazol-2ilo, 5-dimetilamino-1,3,4-oxadiazol-2il o 5-metilamino-1,3,4-tiadiazol-2-ilo, donde la línea ondulada indica el punto de unión al resto de la molécula. La notación  significa que Y^1 puede estar unido al resto de la molécula en cualquiera de las posiciones disponibles del grupo Y^1 establecido anteriormente. Por ejemplo,  significa que está incluido 5H-pirrolo[3,2-c]pirimidin-2-il, 5H-pirrolo[3,2-c]pirimidin-4-il, 5H-pirrolo[3,2-c]pirimidin-5-ilo, 5H-pirrolo[3,2-c]pirimidin-6-ilo y 5H-pirrolo[3,2-c]pirimidin-7-ilo (es decir, las sustituciones pueden ser en las posiciones 2, 4, 5, 6, o 7 del anillo 5H-pirrolo[3,2-c]pirimidina). Todas las otras variables Y^2, Q, Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0078] En algunas realizaciones de compuestos de fórmula (I) y^1 es seleccionado de:

 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,

 , o  , cada uno de los cuales es sustituido opcionalmente con 1 a 3 R^1 sustituyentes; o 1 a 3 sustituyentes R^a; o 1 a 3 sustituyentes R^b; o 1 a 3 sustituyentes R^c; o 1 a 3 sustituyentes R^d; o 1 a 3 sustituyentes R^e; 1 a 3 sustituyentes R^f; o 1 a 3 sustituyentes seleccionados de F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino, 1-hidroxi-1-metiletilo, metilcarbamoilo, 1-carboxiciclopropilo, 1-carbamoilociclopropilo, 1-metoxicarbonilociclopropilo, 1-cianoisopropilo, 1-hidroxiciclopropilo, 1-hidroxiisopropilo, ciclobutoxi, ciclopentoxi, cicloheiloxi, 4-morfolino, 4-hidroxipiperidinilo,1- piperidinilo, piperacinilo, 4-metilpiperacinilo, 4-t-butoxicarbonilopiperacinilo, azetidinilo, pirrolidinilo, ciclopropilocarbamoilo, 5-metil-1,2,4-oxadiazol-3-ilo, 5-metil-1,3,4-oxadiazol-2il, 5-dimetilamino-1,3,4-oxadiazol-2ilo o 5-metilamino-1,3,4-tiadiazol-2-ilo, donde la línea ondulada indica

el punto de unión al resto de la molécula. La notación —≋– significa que Y^1 puede estar unido al resto de la molécula en cualquiera de las posiciones disponibles del grupo Y^1 establecido anteriormente. Por ejemplo,  significa que está incluido 5H-pirrolo[2,3-b]piracin-2-il, 5H-pirrolo[2,3-b]piracin-3-il, 5H-pirrolo[2,3-b]piracin-5-ilo, 5H-pirrolo[2,3-b]piracin-6-ilo, 5H-pirrolo[2,3-b]piracin-7-ilo, (es decir, las sustituciones pueden ser en las posiciones 2, 3, 5, 6, o 7 del anillo de 5H-pirrolo[2,3-b]piracina). Todas las otras variables Y^2, Q, Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0079] En algunas realizaciones de compuestos de fórmula (I) y^1 es CN, halógeno, –OH, C_{1-6} alquilo sustituido opcionalmente, C_{1-6} alcoxi sustituido opcionalmente, C_{1-6}haloalquilo sustituido opcionalmente, o C_{1-6}haloalcoxi sustituido opcionalmente. En otras realizaciones y^1 es CN, halógeno, –OH, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6}haloalquilo o C_{1-6}haloalcoxi, cada uno de los cuales es sustituido opcionalmente con 1 a 3 sustituyentes R^1; o 1 a 3 sustituyentes R^a; o 1 a 3 sustituyentes R^b; o 1 a 3 sustituyentes R^c; o 1 a 3 sustituyentes R^d; o 1 a 3 sustituyentes R^e; 1 a 3 sustituyentes R^f; o 1 a 3 sustituyentes seleccionados de F, Cl, Br, I, –CN, –OH, $–CF_3$, NH_2, $CF_3O–$, $CH_3–$, CH_3O, $–NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino,

1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido o metilcarbamoilo. En algunas realizaciones y^1 es CN, halógeno, -OH, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6}haloalquilo o C_{1-6}haloalcoxi. En otras realizaciones y^1 es CN, Cl, Br, F, I, -OH, $-OCH_3$, $-CF_3$, o $-OCF_3$, cada uno de los cuales es sustituido opcionalmente con 1 a 3 sustituyentes R^1; o 1 a 3 sustituyentes R^a; o 1 a 3 sustituyentes R^b; o 1 a 3 sustituyentes R^c; o 1 a 3 sustituyentes R^d; o 1 a 3 sustituyentes R^e; 1 a 3 sustituyentes R^f; o 1 a 3 sustituyentes seleccionados de F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino, 1-hidroxi-1-metiletilo, metilcarbamoilo, 1-carboxiciclopropilo, 1-carbamoilociclopropilo, 1-metoxicarbonilociclopropilo, 1-cianoisopropilo, 1-hidroxiciclopropilo, 1-hidroxiisopropilo, ciclobutoxi, ciclopentoxi, cicloheiloxi, 4-morfolino, 4-hidroxipiperidinilo,1- piperidinilo, piperacinilo, 4-metilpiperacinilo, 4-t-butoxicarbonilopiperacinilo, azetidinilo, pirrolidinilo, ciclopropilocarbamoilo, 5-metil-1,2,4-oxadiazol-3-ilo, 5-metil-1,3,4-oxadiazol-2il, 5-dimetilamino-1,3,4-oxadiazol-2ilo o 5-metilamino-1,3,4-tiadiazol-2-ilo, En otras realizaciones y^1 es CN, halógeno, -OH, CH_3, CH_3O-, CF_3, CF_3O, ciclopropilo o ciclopro-

pilometilo. Todas las otras variables Y^2, Q, Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0080] Cualquiera de las realizaciones de compuestos de fórmula (I) anteriores y descritas en el presente documento, donde corresponda, cada R^1 es seleccionado por separado de halógeno, –CN, –OH, $–CF_3$, $CF_3O–$, C_{1-6}alquilo, C_{1-6}alcoxi, C_{3-6}cicloalcoxi, $–NO_2$, bencilo, fenilo, ciclopropilo, ciclopropilometilo, 1-cicanociclopropilo, 1-carboxiciclopropilo, 1-carbamoilociclopropilo, 1-metoxicarbonilociclopropilo, 1-cianoisopropilo, 1-hidroxiciclopropilo, 1-hidroxiisopropilo, ciclobutoxi, ciclopentoxi, cicloheiloxi, C_{1-6}alquilo-1,2,4-oxadiazol-3-il, 5-C_{1-6}alquilo-1,3,4-oxadiazol-2il, 5-di(C_{1-6}alquilo)amino-1,3,4-oxadiazol-2il, 5-C_{1-6}alquiloamino-1,3,4-tiadiazol-2-ilo, ciclobutilo, ciclobutilometilo, ciclopentilo, ciclopentilometilo, ciclohexilo, cicloheximetilo, $–OC(O)R^b$, $–C(O)R^b$, $–C(O)OR^b$, $–NHC(O)R^b$, $–C(O)NHR^b$, $–NHR^b$ o $–NR^bR^b$. En ciertos casos, R^1 es F, Cl, Br, I, –CN, –OH, $–CF_3$, NH_2, $CF_3O–$, $CH_3–$, CH_3O, $C_2H_5O–$, $–NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, 1-carboxiciclopropilo, 1-carbamoilociclopropilo, 1-metoxicarbonilociclopropilo, 1-cianoisopropilo, 1-hidroxiciclopropilo, 1-hidroxiisopropilo, ciclobutoxi, ciclopentoxi, cicloheiloxi, 4-morfolino, 4-hidroxipiperidinilo,1- piperidinilo, piperacinilo, 4-metilpiperacinilo, 4-t-

butoxicarbonilopiperacinilo, azetidinilo, pirrolidinilo, ciclopropilocarbamoilo, 5-metil-1,2,4-oxadiazol-3-il, 5-metil-1,3,4-oxadiazol-2ilo, 5-dimetilamino-1,3,4-oxadiazol-2ilo, 1,3,4-tiadiazol-2-ilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, isopropilo, 1-pirrolidinilo, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo.

[0081] En algunas realizaciones de compuestos de fórmula (I) y^1 se selecciona del grupo que consiste en 5-pirimidinilo, 2-pirimidinilo, 4-pirimidinilo, 2-metoxi-5-pirimidinilo, 2-metoxi-3-pirimidinilo, 2-metoxi-4-pirimidinilo, 4-metoxi-2-pirimidinilo, 4-metoxi-4-pirimidinilo, 4-metoxi-5-pirimidinilo, 5-metoxi-2-pirimidinilo, 5-metoxi-4-pirimidinilo, 2-ciclopropilo-5-pirimidinilo, 2-ciclopropilo-3-pirimidinilo, 2-ciclopropilo-4-pirimidinilo, 4-ciclopropilo-2-pirimidinilo, 4-ciclopropilo-4-pirimidinilo, 4-ciclopropilo-5-pirimidinilo, 5-ciclopropilo-2-pirimidinilo, 5-ciclopropilo-4-pirimidinilo, 2-ciclopropilometilo-5-pirimidinilo, 2-ciclopropilometilo-3-pirimidinilo, 2-ciclopropilometilo-4-pirimidinilo, 4-ciclopropilometilo-2-pirimidinilo, 4-ciclopropilometilo-4-pirimidinilo, 4-ciclopropilometilo-5-pirimidinilo, 5-ciclopropilometilo-2-pirimidinilo, 5-ciclopropilometilo-4-pirimidinilo, 2-metil-5-pirimidinilo, 2-metil-3-pirimidinilo, 2-metil-4-pirimidinilo, 4-metil-2-pirimidinilo, 4-metil-4-

pirimidinilo, 4-metil-5-pirimidinilo, 5-metil-2-pirimidinilo, 5-metil-4-pirimidinilo, 2-halo-5-pirimidinilo, 2-halo-3-pirimidinilo, 2-halo-4-pirimidinilo, 4-halo-2-pirimidinilo, 4-halo-4-pirimidinilo, 4-halo-5-pirimidinilo, 5-halo-2-pirimidinilo, 5-halo-4-pirimidinilo, 2-(1-cianociclopropilo)-5-pirimidinilo, 2-(1-cianociclopropilo)-3-pirimidinilo, 2-(1-cianociclopropilo)-4-pirimidinilo, 4-(1-cianociclopropilo)-2-pirimidinilo, 4-(1-cianociclopropilo)-4-pirimidinilo, 4-(1-cianociclopropilo)-5-pirimidinilo, 5-(1-cianociclopropilo)-2-pirimidinilo, 5-(1-cianociclopropilo)-4-pirimidinilo, 2-ciclopropiloamino-5-pirimidinilo, 2-ciclopropiloamino-3-pirimidinilo, 2-ciclopropiloamino-4-pirimidinilo, 4-ciclopropiloamino-2-pirimidinilo, 4-ciclopropiloamino-4-pirimidinilo, 4-ciclopropiloamino-5-pirimidinilo, 5-ciclopropiloamino-2-pirimidinilo, 5-ciclopropiloamino-4-pirimidinilo, 2-dimetilamino-5-pirimidinilo, 2-dimetilamino-3-pirimidinilo, 2-dimetilamino-4-pirimidinilo, 4-dimetilamino-2-pirimidinilo, 4-dimetilamino-4-pirimidinilo, 4-dimetilamino-5-pirimidinilo, 5-dimetilamino-2-pirimidinilo, 5-dimetilamino-4-pirimidinilo, 2-ciano-5-pirimidinilo, 2-ciano-3-pirimidinilo, 2-ciano-4-pirimidinilo, 4-ciano-2-pirimidinilo, 4-ciano-4-pirimidinilo, 4-ciano-5-pirimidinilo, 5-ciano-2-pirimidinilo, 5-ciano-4-pirimidinilo, 2-trifluorometil-5-pirimidinilo, 2-trifluorometil-3-pirimidinilo, 2-trifluorometil-4-pirimidinilo, 4-trifluorometil-2-pirimidinilo, 4-trifluorometil-4-

pirimidinilo, 4- trifluorometil-5-pirimidinilo, 5-trifluorometil-2-pirimidinilo, 5-trifluorometil-4-pirimidinilo, 2-trifluorometoxi-5-pirimidinilo, 2-trifluorometoxi-3-pirimidinilo, 2-trifluorometoxi-4-pirimidinilo, 4-trifluorometoxi-2-pirimidinilo, 4-trifluorometoxi-4-pirimidinilo, 4- trifluorometoxi-5-pirimidinilo, 5-trifluorometoxi-2-pirimidinilo, 5-trifluorometoxi-4-pirimidinilo, 2-hidroxi-5-pirimidinilo, 2-hidroxi-3-pirimidinilo, 2-hidroxi-4-pirimidinilo, 4-hidroxi-2-pirimidinilo, 4-hidroxi-4-pirimidinilo, 4-hidroxi-5-pirimidinilo, 5-hidroxi-2-pirimidinilo, 5-hidroxi-4-pirimidinilo, 2-amino-5-pirimidinilo, 2-amino-3-pirimidinilo, 2-amino-4-pirimidinilo, 4-amino-2-pirimidinilo, 4-amino-4-pirimidinilo, 4-amino-5-pirimidinilo, 5-amino-2-pirimidinilo, 5-amino-4-pirimidinilo, 2-metilamino-5-pirimidinilo, 2-metilamino-3-pirimidinilo, 2-metilamino-4-pirimidinilo, 4-metilamino-2-pirimidinilo, 4-metilamino-4-pirimidinilo, 4-metilamino-5-pirimidinilo, 5-metilamino-2-pirimidinilo, 5-metilamino-4-pirimidinilo, 2-dimetilamino-5-pirimidinilo, 2-dimetilamino-3-pirimidinilo, 2-dimetilamino-4-pirimidinilo, 4-dimetilamino-2-pirimidinilo, 4-dimetilamino-4-pirimidinilo, 4-dimetilamino-5-pirimidinilo, 5-dimetilamino-2-pirimidinilo, 5-dimetilamino-4-pirimidinilo, 2-acetamido-5-pirimidinilo, 2-acetamido-3-pirimidinilo, 2-acetamido-4-pirimidinilo, 4-acetamido-2-pirimidinilo, 4-acetamido-4-pirimidinilo, 4-acetamido-5-

pirimidinilo, 5-acetamido-2-pirimidinilo, 5-acetamido-4-pirimidinilo, 2-metiltio-5-pirimidinilo, 2-metiltio-3-pirimidinilo, 2-metiltio-4-pirimidinilo, 4-metiltio-2-pirimidinilo, 4-metiltio-4-pirimidinilo, 4-metiltio-5-pirimidinilo, 5-metiltio-2-pirimidinilo, 5-metiltio-4-pirimidinilo, 2-acetoxi-5-pirimidinilo, 2-acetoxi-3-pirimidinilo, 2-acetoxi-4-pirimidinilo, 4-acetoxi-2-pirimidinilo, 4-acetoxi-4-pirimidinilo, 4-acetoxi-5-pirimidinilo, 5-acetoxi-2-pirimidinilo, 5-acetoxi-4-pirimidinilo, 2-acetilo-5-pirimidinilo, 2-acetilo-3-pirimidinilo, 2-acetilo-4-pirimidinilo, 4-acetilo-2-pirimidinilo, 4-acetilo-4-pirimidinilo, 4-acetilo-5-pirimidinilo, 5-acetilo-2-pirimidinilo, 5-acetilo-4-pirimidinilo, 2-metoxicarbonilo-5-pirimidinilo, 2-metoxicarbonilo-3-pirimidinilo, 2-metoxicarbonilo-4-pirimidinilo, 4-metoxicarbonilo-2-pirimidinilo, 4-metoxicarbonilo-4-pirimidinilo, 4-metoxicarbonilo-5-pirimidinilo, 5-metoxicarbonilo-2-pirimidinilo, 5-metoxicarbonilo-4-pirimidinilo, 2-metilcarbamoilo-5-pirimidinilo, 2-metilcarbamoilo-3-pirimidinilo, 2-metilcarbamoilo-4-pirimidinilo, 4-metilcarbamoilo-2-pirimidinilo, 4-metilcarbamoilo-4-pirimidinilo, 4-metilcarbamoilo-5-pirimidinilo, 5-metilcarbamoilo-2-pirimidinilo, 5-metilcarbamoilo-4-pirimidinilo, 2-piridilo, 3-piridilo, 4-piridilo, 5-piridilo, 3-metoxi-2-piridilo, 4-metoxi-

2-piridilo, 5-metoxi-2-piridilo, 6-metoxi-2-piridilo, 2-metoxi-3-piridilo, 4-metoxi-3-piridilo, 5-metoxi-3-piridilo, 6-metoxi-3-piridilo, 2-metoxi-4-piridilo, 3-metoxi-4-piridilo, 3-halo-2-piridilo, 4-halo-2-piridilo, 5-halo-2-piridilo, 6-halo-2-piridilo, 2-halo-3-piridilo, 4-halo-3-piridilo, 5-halo-3-piridilo, 6-halo-3-piridilo, 2-halo-4-piridilo, 3-halo-4-piridilo, 3-ciano-2-piridilo, 4-ciano-2-piridilo, 5-caino-2-piridilo, 6-ciano-2-piridilo, 2-ciano-3-piridilo, 4-ciano-3-piridilo, 5-ciano-3-piridilo, 6-ciano-3-piridilo, 2-ciano-4-piridilo, 3-ciano-4-piridilo, 3-hidroxi-2-piridilo, 4-hidroxi-2-piridilo, 5-hidroxi-2-piridilo, 6-hidroxi-2-piridilo, 2-hidroxi-3-piridilo, 4-hidroxi-3-piridilo, 5-hidroxi-3-piridilo, 6-hidroxi-3-piridilo, 2-hidroxi-4-piridilo, 3-hidroxi-4-piridilo, 3-trifluorometil-2-piridilo, 4-trifluorometil-2-piridilo, 5-trifluorometil-2-piridilo, 6-trifluorometil-2-piridilo, 2-trifluorometil-3-piridilo, 4-trifluorometil-3-piridilo, 5-trifluorometil-3-piridilo, 6-trifluorometil-3-piridilo, 2-trifluorometil-4-piridilo, 3-trifluorometil-4-piridilo, 3-amino-2-piridilo, 4-amino-2-piridilo, 5-amino-2-piridilo, 6-amino-2-piridilo, 2-amino-3-piridilo, 4-amino-3-piridilo, 5-amino-3-piridilo, 6-amino-3-piridilo, 2-amino-4-piridilo, 3-amino-4-piridilo, 3-trifluorometoxi-2-piridilo, 4-trifluorometoxi-2-piridilo, 5-trifluorometoxi-2-piridilo, 6-trifluorometoxi-2-piridilo, 2-trifluorometoxi-3-piridilo, 4-trifluorometoxi-3-piridilo, 5-trifluorometoxi-3-piridilo, 6-trifluorometoxi-3-

piridilo, 2-trifluorometoxi-4-piridilo, 3-trifluorometoxi-4-piridilo, 3-metil-2-piridilo, 4-metil-2-piridilo, 5-metil-2-piridilo, 6-metil-2-piridilo, 2-metil-3-piridilo, 4-metil-3-piridilo, 5-metil-3-piridilo, 6-metil-3-piridilo, 2-metil-4-piridilo, 3-metil-4-piridilo, 3-metoxi-2-piridilo, 4-metoxi-2-piridilo, 5-metoxi-2-piridilo, 6-metoxi-2-piridilo, 2-metoxi-3-piridilo, 4-metoxi-3-piridilo, 5-metoxi-3-piridilo, 6-metoxi-3-piridilo, 2-metoxi-4-piridilo, 3-metoxi-4-piridilo, 3-ciclopropilo-2-piridilo, 4-ciclopropilo-2-piridilo, 5-ciclopropilo-2-piridilo, 6-ciclopropilo-2-piridilo, 2-ciclopropilo-3-piridilo, 4-ciclopropilo-3-piridilo, 5-ciclopropilo-3-piridilo, 6-ciclopropilo-3-piridilo, 2-ciclopropilo-4-piridilo, 3-ciclopropilo-4-piridilo, 3-ciclopropilometilo-2-piridilo, 4-ciclopropilometilo-2-piridilo, 5-ciclopropilometilo-2-piridilo, 6-ciclopropilometilo-2-piridilo, 2-ciclopropilometilo-3-piridilo, 4-ciclopropilometilo-3-piridilo, 5-ciclopropilometilo-3-piridilo, 6-ciclopropilometilo-3-piridilo, 2-ciclopropilometilo-4-piridilo, 3-ciclopropilometilo-4-piridilo, 3-ciclopropiloamino-2-piridilo, 4-ciclopropiloamino-2-piridilo, 5-ciclopropiloamino2-piridilo, 6-ciclopropiloamino-2-piridilo, 2-ciclopropiloamino-3-piridilo, 4-ciclopropiloamino-3-piridilo, 5-ciclopropiloamino-3-piridilo, 6-ciclopropiloamino-3-piridilo, 2-ciclopropiloamino-4-piridilo, 3-ciclopropiloamino-4-piridilo, 3-ciclopropilometiloamino-2-piridilo, 4-ciclopropilometiloamino-2-piridilo, 5-

ciclopropilometiloamino-2-piridilo, 6-ciclopropilometiloamino-2-piridilo, 2-ciclopropilometiloamino-3-piridilo, 4-ciclopropilometiloamino-3-piridilo, 5-ciclopropilometiloamino-3-piridilo, 6-ciclopropilometiloamino-3-piridilo, 2-ciclopropilometiloamino-4-piridilo, 3-ciclopropilometiloamino-4-piridilo, 3-metilamino-2-piridilo, 4-metilamino-2-piridilo, 5-metilamino-2-piridilo, 6-metilamino-2-piridilo, 2-metilamino-3-piridilo, 4-metilamino-3-piridilo, 5-metilamino-3-piridilo, 6-metilamino-3-piridilo, 2-metilamino-4-piridilo, 3-metilamino-4-piridilo, 3-dimetilamino-2-piridilo, 4-dimetilamino-2-piridilo, 5-dimetilamino-2-piridilo, 6-dimetilamino-2-piridilo, 2-dimetilamino-3-piridilo, 4-dimetilamino-3-piridilo, 5-dimetilamino-3-piridilo, 6-dimetilamino-3-piridilo, 2-dimetilamino-4-piridilo, 3-dimetilamino-4-piridilo, 3-metiltio-2-piridilo, 4-metiltio-2-piridilo, 5-metiltio-2-piridilo, 6-metiltio-2-piridilo, 2-metiltio-3-piridilo, 4-metiltio-3-piridilo, 5-metiltio-3-piridilo, 6-metiltio-3-piridilo, 2-metiltio-4-piridilo, 3-metiltio-4-piridilo, 3-acetoxi-2-piridilo, 4-acetoxi-2-piridilo, 5-acetoxi-2-piridilo, 6-acetoxi-2-piridilo, 2-acetoxi-piridilo, 4-acetoxi-3-piridilo, 5-acetoxi-3-piridilo, 6-acetoxi-3-piridilo, 2-acetoxi-4-piridilo, 3-acetoxi-4-piridilo, 3-acetilo-2-piridilo, 4-acetilo-2-piridilo, 5-acetilo-2-piridilo, 6-acetilo-2-piridilo, 2-acetilo-piridilo, 4-acetilo-3-piridilo, 5-acetilo-3-piridilo, 6-acetilo-3-piridilo, 2-acetilo-4-piridilo, 3-acetilo-4-piridilo, 3-

metoxicarbonilo-2-piridilo, 4-metoxicarbonilo-2-piridilo, 5-metoxicarbonilo-2-piridilo, 6-metoxicarbonilo-2-piridilo, 2-metoxicarbonilo-3-piridilo, 4-metoxicarbonilo-3-piridilo, 5-metoxicarbonilo-3-piridilo, 6-metoxicarbonilo-3-piridilo, 2-metoxicarbonilo-4-piridilo, 3-metoxicarbonilo-4-piridilo, 3-metilcarbamoilo-2-piridilo, 4-metilcarbamoilo-2-piridilo, 5-metilcarbamoilo-2-piridilo, 6-metilcarbamoilo-2-piridilo, 2-metilcarbamoilo-3-piridilo, 4-metilcarbamoilo-3-piridilo, 5-metilcarbamoilo-3-piridilo, 6-metilcarbamoilo-3-piridilo, 2-metilcarbamoilo-4-piridilo, 3-metilcarbamoilo-4-piridilo, 3-acetamido-2-piridilo, 4-acetamido-2-piridilo, 5-acetamido-2-piridilo, 6-acetamido-2-piridilo, 2-acetamido-3-piridilo, 4-acetamido-3-piridilo, 5-acetamido-3-piridilo, 6-acetamido-3-piridilo, 2-acetamido-4-piridilo y 3-acetamido-4-piridilo, 3-(1-cianociclopropilo)-2-piridilo, 4-(1-cianociclopropilo)-2-piridilo, 5-(1-cianociclopropilo)-2-piridilo, 6-(1-cianociclopropilo)-2-piridilo, 2-(1-cianociclopropilo)-3-piridilo, 4-(1-cianociclopropilo)-3-piridilo, 5-(1-cianociclopropilo)-3-piridilo, 6-(1-cianociclopropilo)-3-piridilo, 2-(1-cianociclopropilo)-4-piridilo, 3-(1-cianociclopropilo)-4-piridilo, cada uno de los cuales es sustituido opcionalmente con 1, 2, o 3 sustituyentes seleccionados por separado de F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, 1-cianociclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, metilamino, di-

metilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, isopropilo, 1-pirrolidinilo, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo. En algunos casos, los sustituyentes 1, 2, 3 están en la porción aromática de Y^1. En otros casos, los sustituyentes 1, 2, 3 están en la porción alifática de Y^1. Todas las otras variables Y^2, Q, Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0082] En ciertas realizaciones de compuestos de fórmula (I) y^1 es fenilo sustituido con 1 a 2 sustituyentes seleccionados por separado de F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, C_2H_5O-, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, 1-carboxiciclopropilo, 1-carbamoilociclopropilo, 1-metoxicarbonilociclopropilo, 1-cianoisopropilo, 1-hidroxiciclopropilo, 1-hidroxiisopropilo, ciclobutoxi, ciclopentoxi, cicloheiloxi, 4-morfolino, 4-hidroxipiperidinilo,1- piperidinilo, piperacinilo, 4-metilpiperacinilo, 4-t-butoxicarbonilopiperacinilo, azetidinilo, pirrolidinilo, ciclopropilocarbamoilo, 5-metil-1,2,4-oxadiazol-3-il, 5-metil-1,3,4-oxadiazol-2ilo, 5-dimetilamino-1,3,4-oxadiazol-2ilo, 5-metilamino-1,3,4-tiadiazol-2-ilo, metilamino metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, isopropilo, 1-pirrolidinilo, 1-

ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo.

[0083] En otras realizaciones de compuestos de fórmula (I) y^1 se selecciona del grupo que consiste en fenilo, 2-halofenilo, 3-halofenilo, 4-halofenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-cianofenilo, 3-cianofenilo, 4-cianofenilo, 2-hidroxifenilo, 3-hidroxifenilo, 4-hidroxifenilo, 2-trifluorometilfenilo, 3-trifluorometilfenilo, 4-trifluorometilfenilo, 2-aminofenilo, 3-aminofenilo, 4-aminofenilo, 2-trifluorometilfenilo, 3-trifluorometilfenilo, 4-trifluorometilfenilo, 2-metilfenilo, 3-metilfenilo, 4-metilfenilo, 2-metoxifenilo, 3-metoxifenilo, 4-metoxifenilo, 2-ciclopropilofenilo, 3-ciclopropilofenilo, 4-ciclopropilofenilo, 2-ciclopropilometilofenilo, 3- ciclopropilometilofenilo, 4-ciclopropilometilofenilo, 2-ciclopropilometiloaminofenilo, 3-ciclopropilometiloaminofenilo, 4-ciclopropilometiloaminofenilo, 2-ciclopropiloaminofenilo, 3-ciclopropiloaminofenilo, 4-ciclopropiloaminofenilo, 2-metilaminofenilo, 3-metilaminofenilo, 4-metilaminofenilo, 2-dimetilaminofenilo, 3-dimetilaminofenilo, 4-dimetilaminofenilo, 2-metiltiofenilo, 3-metiltiofenilo, 4-metiltiofenilo, 2-acetoxifenilo, 3-acetoxifenilo, 4-acetoxifenilo, 2-acetilofenilo, 3-acetilofenilo, 4-acetilofenilo, 2-metoxicarbonilofenilo, 3-metoxicarbonilofenilo, 4-metoxicarbonilofenilo, 2-acetamidofenilo, 3-acetamidofenilo, 4-acetamidofenilo, 2-metilcarbamoilofenilo, 3-

metilcarbamoilofenilo, 4-metilcarbamoilofenilo, 2-(1-cianociclopropilo)fenilo, 3-(1-cianociclopropilo)fenilo y 4-(1-cianociclopropilo)fenilo, cada uno de los cuales es sustituido opcionalmente con 1, 2 o sustituyentes seleccionados por separado de F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, 1-cianociclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo o metilcarbamoilo. En algunos casos, los sustituyentes 1, 2, 3 sustituyentes están en la porción aromática de Y^1. En otros casos, los sustituyentes 1, 2, 3 están en la porción alifática de Y^1. Todas las otras variables Y^2, Q, Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0084] En algunas realizaciones de compuestos de fórmula (I) y^2 ha sido definido en el resumen de la invención y las otras variables Y^1, Q y Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones anteriores y cualquiera de las realizaciones descritas en este documento.

[0085] En algunas realizaciones de compuestos de fórmula (I) y^2 es H, halógeno, CN, C_{1-6}alquilo, C_{1-6}alcoxi, C_{3-6}cicloalquiloamino, C_{3-6}cicloalquilo-C_{1-3}alquiloamino, arilo, heteroarilo, ariloalquilo o heteroariloalquilo, donde la porción

alifática o aromática de Y^2 es sustituido opcionalmente con 1, 2 o 3 sustituyentes seleccionados por separado de H, F, Cl, I, CN, CH_3, CH_3O–, fenilo, CF_3 o CF_3O. En ciertos casos y^2 es H, halógeno, CN, C_{1-6}alquilo, C_{1-6}alcoxi, C_{3-6}cicloalquiloamino o C_{3-6}cicloalquilo–C_{1-3}alquiloamino, donde la porción alifática de Y^2 es sustituida opcionalmente con 1, 2 o 3 sustituyentes seleccionados por separado de H, F, Cl, I, CN, CH_3, CH_3O–, fenilo, CF_3 o CF_3O. Todas las otras variables Y^1, Q y Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0086] En algunas realizaciones de compuestos de fórmula (I) y^2 es H, F, Cl, I, CN, CH_3, CH_3O–, ciclopropiloamino o ciclopropilometiloamino. Todas las otras variables Y^1, Q y Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0087] En algunas realizaciones preferidas de compuestos de fórmula (I) y^2 es H y todas las otras variables Y^1, Q y Z de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0088] En algunas realizaciones de compuestos de fórmula (I), Q es seleccionado de H, F, Cl o CH_3. En una realización, Q es H. En otra realización, Q es F. En otra realización adicional, Q es CH_3. En otra realización adicional, Q es Cl. En otra realización, Q es H o F. Todas las otras variables Y^1 y^2, Z de fórmula (I) y

R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0089] En algunas realizaciones de compuestos de fórmula (I), Z ha sido definido en el resumen de la invención. Todas las otras variables de fórmula (I) y R^4, R^5, R^6, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0090] En algunas realizaciones de compuestos de fórmula (I), Z es $-N(R^4)(R^5)$ o $-C(R^6)(R^7)(R^8)$, donde R^4 y R^5 son seleccionados cada uno por separado del grupo que consiste en H, sustituido opcionalmente C_{1-6}alquilo, sustituido opcionalmente C_{3-8}cicloalquilo, sustituido opcionalmente C_{3-8}cicloalquiloalquilo, sustituido opcionalmente heterocicloalquilo, sustituido opcionalmente heterocicloalquiloalquilo, sustituido opcionalmente arilo, sustituido opcionalmente ariloalquilo, sustituido opcionalmente heteroarilo y sustituido opcionalmente heteroariloalquilo; o R^4 y R^5 tomados junto con el átomo de nitrógeno al cual están unidos forman un anillo de cuatro a ocho miembros que tiene de 0-2 heteroátomos adicionales como miembros de anillo seleccionados de N, O o S, donde el anillo de cuatro a ocho miembros es sustituido opcionalmente con uno a tres grupos seleccionados por separado de C_{1-6} haloalquilo, C_{1-6} haloalcoxi, C_{1-6} alquilo, C_{3-8} cicloalquilo, C_{3-8} cicloalquiloalquilo, arilo, ariloalquilo o R^e. R^6, R^7 y R^8 son cada uno por separado H, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, C_{3-8} cicloalquilo, C_{3-8} ci-

cloalquiloalquilo, arilo, ariloalquilo, heterocicloalquilo, heterocicloalquiloalquilo, heteroarilo, heteroariloalquilo o $-X^2R^9$; donde la porción alifática o aromática de R^6, R^7 y R^8 es cada una sustituida opcionalmente con 1 a 3 miembros seleccionados por separado del grupo que consiste en C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heterocicloalquilo, heterocicloalquiloalquilo, heteroarilo, heteroariloalquilo y R^e; o dos opciones cualesquiera de los grupos R^6, R^7 y R^8 grupos tomados junto con el átomo de carbono al cual están unidos forman un anillo carbocíclico de 3 a 8 miembros o un anillo heterocíclico de 4 a 8 miembros que tiene de 1 a 2 heteroátomos como miembros de anillo seleccionados de N, O o S, donde el anillo carbocíclico de 3 a 8 miembros o el anillo heterocíclico de 4 a 8 miembros es sustituido opcionalmente con uno a tres grupos seleccionados por separado de C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo o heteroariloalquilo o R^e, proporcionado en cada aparición, como mínimo dos opciones cualesquiera de los grupos R^6, R^7 y R^8 grupos no son simultáneamente hidrógeno. Todas las otras variables Y^1 y^2 y Q de fórmula (I) han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0091] En algunas realizaciones de compuestos de fórmula (I), Z es $-N(R^4)(R^5)$, donde R^4 y R^5 son seleccionados cada uno por separado de C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, arilo-C_{1-4}alquilo, heteroarilo o heteroarilo-C_{1-4}alquilo,

cada uno de los cuales es sustituido opcionalmente con (i) 1-3 sustituyentes seleccionados por separado de C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo o R^e; o (ii) 1, 2 o 3 sustituyentes R^a; o (iii) 1, 2 o 3 sustituyentes R^b; o (iv) 1, 2 o 3 sustituyentes R^c; o (v) 1, 2 o 3 sustituyentes R^d; o (vi) 1, 2 o 3 grupos R^f. Todas las otras variables Y^1 y ^{2} y Q de fórmula (I) han sido definidos en cualquiera de las realizaciones descritas en este documento.

[0092] En algunas realizaciones de compuestos de fórmula (I), R^4 es $-CH_3$ y R^5 es C_{2-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, arilo-C_{1-4}alquilo, heteroarilo o heteroarilo-C_{1-4}alquilo, cada uno de los cuales es sustituido opcionalmente con (i) 1-3 sustituyentes seleccionados por separado de C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo o R^e; o (ii) 1, 2 o 3 sustituyentes R^a; o (iii) 1, 2 o 3 sustituyentes R^b; o (iv) 1, 2 o 3 sustituyentes R^c; o (v) 1, 2 o 3 sustituyentes R^d; o (vi) 1, 2 o 3 grupos R^f. En ciertos casos, R^4 es $-CH_3$ y R^5 es C_{2-6}alquilo. Todas las otras variables Y^1 y ^{2} y Q de fórmula (I) han sido definidos en cualquiera de las realizaciones descritas en este documento.

[0093] En algunas realizaciones de compuestos de fórmula (I), R^4 y R^5 son seleccionados cada uno por separado de C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, arilo-C_{1-4}alquilo,

heteroarilo o heteroarilo-C_{1-4}alquilo, cada uno de los cuales es sustituido opcionalmente con 1, 2 o 3 R^x miembros seleccionados de F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-piridilometilo, 3-piridilometilo, 4-piridilometilo, 2-oxetanilo, 3-oxtetanilo, 2-oxetanilometilo, 3-oxtetanilometilo, 2-tetrahidrofuranilo, 3-tetrahidrofuranilo, 2-tetrahidrofuranilometilo, 3-tetrahidrofuranilometilo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-tetrahidrotiofenilo, 3-tetrahidrotiofenilo, 4-morfolinilo, 2-morfolinilo o 3- morfolinilo. En ciertos casos, R^x es F, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-piridilometilo, 3-piridilometilo, 4-piridilometilo, 2-oxetanilo, 3-oxtetanilo, 2-oxetanilometilo, 3-oxtetanilometilo, 2-tetrahidrofuranilo, 3-tetrahidrofuranilo, 2-tetrahidrofuranilometilo, 3-tetrahidrofuranilometilo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-tetrahidrotiofenilo, 3-tetrahidrotiofenilo, 4-morfolinilo, 2-morfolinilo o 3- morfolinilo. Todas las otras

variables Y^1 y^2 y Q de fórmula (I) han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0094] En algunas realizaciones de compuestos de fórmula (I), R^4 es $-CH_3$ y R^5 es C_{2-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, arilo-C_{1-4}alquilo, heteroarilo o heteroarilo-C_{1-4}alquilo, cada uno de los cuales es sustituido opcionalmente con 1, 2 o 3 R^x miembros seleccionados de F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-piridilometilo, 3-piridilometilo, 4-piridilometilo, 2-oxetanilo, 3-oxtetanilo, 2-oxetanilometilo, 3-oxtetanilometilo, 2-tetrahidrofuranilo, 3-tetrahidrofuranilo, 2-tetrahidrofuranilometilo, 3-tetrahidrofuranilometilo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-tetrahidrotiofenilo, 3-tetrahidrotiofenilo, 4-morfolinilo, 2-morfolinilo o 3- morfolinilo. En ciertos casos, R^x es F, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-piridilometilo, 3-piridilometilo, 4-piridilometilo, 2-oxetanilo, 3-oxtetanilo, 2-oxetanilometilo, 3-oxtetanilometilo, 2-tetrahidrofuranilo, 3-

tetrahidrofuranilo, 2-tetrahidrofuranilometilo, 3-tetrahidrofuranilometilo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-tetrahidrotiofenilo, 3-tetrahidrotiofenilo, 4-morfolinilo, 2-morfolinilo o 3- morfolinilo. Todas las otras variables Y^1 y^2 y Q de fórmula (I) han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0095] En algunas realizaciones de compuestos de fórmula (I), R^4 es $-CH_3$ y R^5 es seleccionado de etilo, propilo, butilo, pentilo, ciclopropilo, ciclopropilometilo, ciclobutilo, ciclobutilometilo, ciclopentilo, ciclopentilometilo, ciclohexilo, ciclohexilometilo, fenilo o bencilo, cada uno de los cuales es sustituido opcionalmente con 1-3 sustituyentes seleccionados por separado de F, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-piridilometilo, 3-piridilometilo, 4-piridilometilo, 2-oxetanilo, 3-oxtetanilo, 2-oxetanilometilo, 3-oxtetanilometilo, 2-tetrahidrofuranilo, 3-tetrahidrofuranilo, 2-tetrahidrofuranilometilo, 3-tetrahidrofuranilometilo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-tetrahidrotiofenilo, 3-tetrahidrotiofenilo, 4-morfolinilo, 2-morfolinilo o 3-morfolinilo. Todas las otras variables Y^1 y^2 y Q de fórmula (I) han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0096] En algunas realizaciones de compuestos de fórmula (I), Z es $-N(R^4)(R^5)$, donde $-N(R^4)(R^5)$ es seleccionado de 1-azetindinilo, 1-pirrolidinilo, 1-piperidinilo, 4-morfolinilo, 4-tiomorfolinilo, 3-oxazolidinilo, 3-tiazolidinilo, 2-isoxazolidinilo, 2-isotiazolidinilo, 1-pirazolidinilo, 1-piperacinilo, 1-hexahidropirimidinilo o 1-hexahidropiridacinilo, cada uno de los cuales es (i) sustituido opcionalmente con 1 a 3 R^{26} sustituyentes seleccionados por separado del grupo que consiste en halógeno, C_{1-6}alquilo, C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, heterocicloalquilo, heterocicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo y R^c; o (ii) dos sustituyentes adyacentes R^{26} junto con el átomo al cual están unidos forman un anillo aromático de 5 o 6 miembros que tiene de 0 a 2 átomos adicionales como miembros de anillo seleccionados de O, N o S o (iii) sustituido opcionalmente con 1 a 8 deuterios con como mínimo 52,5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99,5% o 99,9% de incorporación de deuterio por cada deuterio. En ciertos casos, R^{26} es F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O–, CH_3–, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-piridilometilo, 3-piridilometilo, 4-piridilometilo, 2-oxetanilo, 3-oxtetanilo, 2-oxetanilometilo, 3-oxtetanilometilo,

2-tetrahidrofuranilo, 3-tetrahidrofuranilo, 2-tetrahidrofuranilometilo, 3-tetrahidrofuranilometilo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-tetrahidrotiofenilo, 3-tetrahidrotiofenilo, 4-morfolinilo, 2-morfolinilo o 3- morfolinilo. En otros casos, R^{26} es F, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-piridilometilo, 3-piridilometilo, 4-piridilometilo, 2-oxetanilo, 3-oxtetanilo, 2-oxetanilometilo, 3-oxtetanilometilo, 2-tetrahidrofuranilo, 3-tetrahidrofuranilo, 2-tetrahidrofuranilometilo, 3-tetrahidrofuranilometilo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-tetrahidrotiofenilo, 3-tetrahidrotiofenilo, 4-morfolinilo, 2-morfolinilo o 3- morfolinilo. En otros casos, R^{26} es F, CH_3, metoxicarbonilo, etoxicarbonilo, $-CH_3$, $CH_3(CO)NH-$, vinilo, propen-3-ilo o $CH_3(CO)(CH_3)N-$. En algunas realizaciones, cada átomo de hidrógeno en Z es remplazado opcionalmente por un átomo de deuterio con como mínimo 52,5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99,5% o 99,9% de incorporación de deuterio por cada deuterio. Todas las otras variables Y^1 y^2 y Q de fórmula (I) han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0097] En algunas realizaciones de compuestos de fórmula (I), Z es $-C(R^6)(R^7)(R^8)$, donde R^6 es H y R^7 y R^8 son cada uno por separado C_{1-6}alquilo, sustituido opcionalmente con 1 a 3 R^d o R^e. En algunas realizaciones, R^6, R^7 y R^8 son cada uno por separado C_{1-6}alquilo, sustituido opcionalmente con 1 a 3 R^d o R^e. En algunas realizaciones, $-C(R^6)(R^7)(R^8)$ es ciclopropilo, ciclobutilo, ciclohexilo, ciclopentilo, cicloheptilo, ciclooctilo, cada uno de los cuales es sustituido opcionalmente con 1-3 R^{28} sustituyentes seleccionados por separado de F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-CH_2CH=CH_2$, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, vinilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-piridilometilo, 3-piridilometilo, 4-piridilometilo, 2-oxetanilo, 3-oxtetanilo, 2-oxetanilometilo, 3-oxtetanilometilo, 2-tetrahidrofuranilo, 3-tetrahidrofuranilo, 2-tetrahidrofuranilometilo, 3-tetrahidrofuranilometilo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-tetrahidrotiofenilo, 3-tetrahidrotiofenilo, 4-morfolinilo, 2-morfolinilo o 3- morfolinilo. En algunos casos, R^{28} es F, –CN, –OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-piridilometilo, 3-

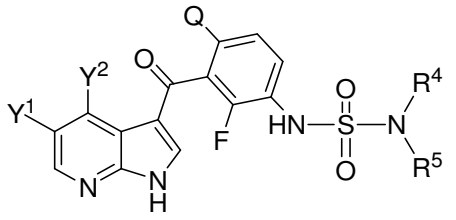
piridilometilo, 4-piridilometilo, 2-oxetanilo, 3-oxtetanilo, 2-oxetanilometilo, 3-oxtetanilometilo, 2-tetrahidrofuranilo, 3-tetrahidrofuranilo, 2-tetrahidrofuranilometilo, 3-tetrahidrofuranilometilo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-tetrahidrotiofenilo, 3-tetrahidrotiofenilo, 4-morfolinilo, 2-morfolinilo o 3- morfolinilo. En algunas realizaciones, $-C(R^6)(R^7)(R^8)$ es 2-azetindinilo, 3-azetindinilo, 3-pirrolidinilo, 2-pirrolidinilo, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo, 2-morfolinilo, 3-morfolinilo, 2-tiomorfolinilo, 3-tiomorfolinilo, 2-oxazolidinilo, 4-oxazolidinilo, 5-oxazolidinilo, 2-tiazolidinilo, 4-tiazolidinilo, 5-tiazolidinilo, 3-isoxazolidinilo, 4-isoxazolidinilo, 5-isoxazolidinilo, 3-isotiazolidinilo, 4-isotiazolidinilo, 5-isotiazolidinilo, 3-pirazolidinilo, 4-pirazolidinilo, 2-piperacinilo, 2-hexahidropirimidinilo, 4-hexahidropirimidinilo, 5-hexahidropirimidinilo, 3-hexahidropiridacinilo o 4-hexahidropiridacinilo, cada uno de los cuales es sustituido opcionalmente con 1 a 3 sustituyentes R^{28}. En algunas realizaciones, cada átomo de hidrógeno en Z es remplazado opcionalmente por un átomo de deuterio con como mínimo 52,5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99,5% o 99,9% de incorporación de deuterio por cada deuterio. Todas las otras variables Y^1 y ^{2} y Q de fórmula (I) han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0098] En algunas realizaciones de compuestos de fórmula (I), Z se selecciona del grupo que consiste en ciclopropilo, ciclobutilo, ciclohexilo, ciclopentilo, cicloheptilo, ciclooctilo, 1-azetindinilo, 1-pirrolidinilo, 1-piperidinilo, 4-morfolinilo, 4-tiomorfolinilo 3-oxazolidinilo, 3-tiazolidinilo, 2-isoxazolidinilo, 2-isotiazolidinilo, 1-pirazolidinilo, 1-piperacinilo, 1-hexahidropirimidinilo, 1-hexahidropiridacinilo, $(CH_3)(CF_3CH_2)N$-, ciclopropilometiloamino, sec-butilo, pentan-2-ilo y pentan-3-ilo, cada uno de los cuales es (i) sustituido opcionalmente con uno a tres sustituyentes R^{27} seleccionados por separado del grupo que consiste en halógeno, C_{1-6}alquilo, C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{1-6}alquilo, C_{3-8} cicloalquilo, C_{3-8} cicloalquiloalquilo, heterocicloalquilo, heterociclo-alquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo y R^c; o (ii) dos sustituyentes adyacentes R^{27} junto con el átomo al cual están unidos forman un anillo aromático de 5 o 6 miembros que tiene de 0 a 2 átomos adicionales como miembros de anillo seleccionados de O, N o S; o (iii) sustituido opcionalmente con 1 a 11 deuterios que tiene como mínimo 52,5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99,5% o 99,9% de incorporación de deuterio por cada deuterio. En una realización, Z es ciclopropilo sustituido opcionalmente con 1 a 2 R^{27} grupos. En otra realización, Z es ciclopentilo sustituido opcionalmente con 1 a 2 grupos R^{27}. En otra realización adicional Z es 1-pirrolidinilo sustituido opcionalmente con 1 a 2 grupos R^{27}. En otra realiza-

ción, Z es 1-piperidinilo sustituido opcionalmente con 1 a 2 grupos R^{27}. En otra realización, Z es 1-pirrolidinilo, 3-fluoro-1-pirrolidinilo, (3S)-3-fluoro-1-pirrolidinilo, (3R)-3-fluoro-1-pirrolidinilo, 3,3-difluoro-1-pirrolidinilo, 3-C_{1-6}alquilo-C(O)-C_{1-6}alquilo-N-1-pirrolidinilo, 3-C_{1-6}alquilo-C(O)NH-1-pirrolidinilo, C_{1-6}alcoxicarbonilo-1-pirrolidinilo o 3,3-dimetil-1-pirrolidinilo. En ciertos casos, R^{27} es F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-piridilometilo, 3-piridilometilo, 4-piridilometilo, 2-oxetanilo, 3-oxtetanilo, 2-oxetanilometilo, 3-oxtetanilometilo, 2-tetrahidrofuranilo, 3-tetrahidrofuranilo, 2-tetrahidrofuranilometilo, 3-tetrahidrofuranilometilo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-tetrahidrotiofenilo, 3-tetrahidrotiofenilo, 4-morfolinilo, 2-morfolinilo o 3- morfolinilo. En un caso, R^{27} es -F, metoxicarbonilo, etoxicarbonilo, $-CH_3$, $CH_3(CO)NH$-, vinilo, propen-3-ilo o $CH_3(CO)(CH_3)N$-. En otro caso, R^{27} es -F, metoxicarbonilo, etoxicarbonilo, $-CH_3$, $CH_3(CO)NH$- o $CH_3(CO)(CH_3)N$-. En otro caso adicional, R^{27} es vinilo o propen-3-ilo. Todas las otras variables Y^1 y^2 y Q de fórmula (I) han sido definidas en cualquiera de las realizaciones descritas en este documento.

Subfórmulas de fórmula I

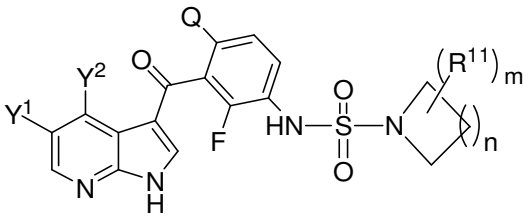
[0099] En una realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Ia):



Ia

donde los sustituyentes Y^1 y^2, Q, R^4 y R^5 han sido definidos en cualquiera de las realizaciones reveladas en el presente documento. En algunas realizaciones, R^4 es CH_3 y R^5 es C_{2-6}alquilo sustituido opcionalmente con 1–3 sustituyentes seleccionados por separado de F, Cl, Br, I, –CN, –OH, $–CF_3$, NH_2, $CF_3O–$, $CH_3–$, CH_3O, $–NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1–cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, 2–piridilo, 3–piridilo, 4–piridilo, 2–piridilometilo, 3–piridilometilo, 4–piridilometilo, 2–oxetanilo, 3–oxtetanilo, 2–oxetanilometilo, 3–oxtetanilometilo, 2–tetrahidrofuranilo, 3–tetrahidrofuranilo, 2–tetrahidrofuranilometilo, 3–tetrahidrofuranilometilo, 1–pirrolidinilo, 2–pirrolidinilo, 3–pirrolidinilo, 2–tetrahidrotiofenilo, 3–tetrahidrotiofenilo, 4–morfolinilo, 2–morfolinilo o 3– morfolinilo.

[0100] En una segunda realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Ib):

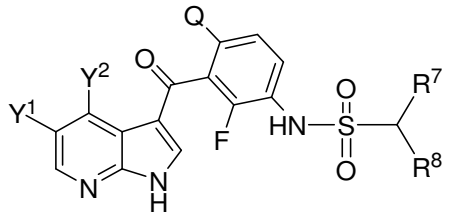


Ib

donde R^{11} es C_{1-6}alquilo, C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, heterocicloalquilo, heterocicloalquiloalquilo o R^e, cada uno de los cuales es sustituido opcionalmente con (i) 1-3 sustituyentes seleccionados por separado de C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, R^d o R^e; o (ii) 1, 2 o 3 sustituyentes R^a; o (iii) 1, 2 o 3 sustituyentes R^b; o (iv) 1, 2 o 3 sustituyentes R^c; o (v) 1, 2 o 3 sustituyentes R^d; o (vi) 1, 2 o 3 grupos R^f; el subíndice n es 1, 2, 3, 4 o 5 y el subíndice m es 0, 1, 2 o 3. En algunas realizaciones, R^{11} es C_{1-6}alquilo, F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, etilo, propilo, butilo, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-piridilometilo, 3-piridilometilo, 4-piridilometilo, 2-oxetanilo, 3-oxtetanilo, 2-oxetanilometilo, 3-oxtetanilometilo, 2-tetrahidrofuranilo, 3-tetrahidrofuranilo, 2-tetrahidrofuranilometilo, 3-tetrahidrofuranilometilo,

1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-tetrahidrotiofenilo, 3-tetrahidrotiofenilo, 4-morfolinilo, 2-morfolinilo o 3- morfolinilo. En algunas realizaciones, m es 0. En otras realizaciones, el subíndice n es 1, 2, 3 o 4. En algunas realizaciones, n es 1, 2 o 3 y m es 1 o 2. Todas las otras variables Y^1 y^2 y Q han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0101] En una tercera realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Ic):

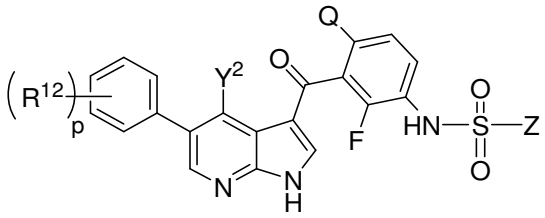


Ic

donde R^7 y R^8 son cada uno por separado C_{1-6}alquilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo o $-X^2R^9$, donde la porción alifática o aromática de R^7 y R^8 es cada una sustituida opcionalmente con 1 a 3 miembros seleccionados por separado del grupo que consiste en C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo y R^e; y donde X^2 es $-NR^{10}$, O o S; R^{10} es H, C_{1-6}alquilo o arilo; y R^9 es H, C_{1-6}alquilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo o heteroariloalquilo, donde R^9 es sustituido opcionalmente con 1 a 3 sustituyentes R^e. En algunas rea-

lizaciones, grupos R^7 y R^8 tomados junto con el átomo de carbono al cual están unidos forman un anillo carbocíclico de 3 a 8 miembros o un anillo heterocíclico de 4 a 8 miembros que tiene de 1 a 2 heteroátomos como miembros de anillo seleccionados de N, O o S, donde el anillo carbocíclico de 3 a 8 miembros o el anillo heterocíclico de 4 a 8 miembros es sustituido opcionalmente con uno a tres grupos seleccionados por separado de C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo o heteroariloalquilo o R^e. Todas las otras variables Y^1 y^2 y Q han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0102] En una cuarta realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Id):

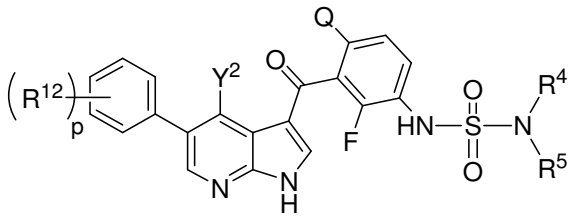


Id

donde R^{12} es H o R^1; o dos grupos adyacentes R^{12} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S; donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1-3 sustituyentes R^d o R^e y el subíndice p es un número entero de 1 a 5. En una realización, p es 1. En otra realización, p es 2. En otra realización adicional, p es

5 y dos sustituyentes adyacentes de R^{12} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S; donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1–3 sustituyentes R^d o R^e y cada R^{12} es por separado H, R^d o R^e. En algunas realizaciones, los dos sustituyentes adyacentes R^{12} junto con los átomos a los cuales están unidos forman un anillo carbocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de benceno, ciclopentano y ciclohexano. Los sustituyentes en el anillo carbocíclico puede ser de 1–2 grupos R^d o R^e. En otras realizaciones, dos sustituyentes adyacentes R^{12} junto con los átomos a los cuales están unidos forman un anillo heterocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de pirrole, furano, tiofeno, pirazole, imidazole, oxazole, isoxazole, tiazole, isotiazole, piridina, piracina, piridazina, tetrahidrofurano, tetrahidropirano, tetrahidrotiofeno, pirazolidina, isoxazolidina, imidazolidina, oxazolidina, tiazolidina, isotiazolidina, piperidina, piperacina y hexahidropirimidina. Todas las otras variables Y^2, Q y Z han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0103] En una quinta realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Id-1):

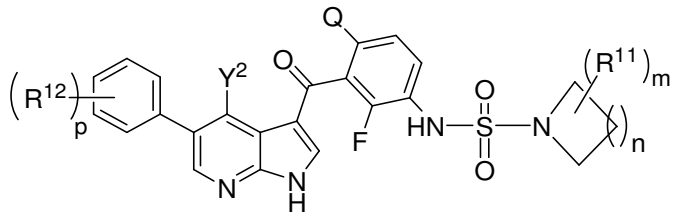


Id-1

donde R^{12} es H o R^1; o dos grupos adyacentes R^{12} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S; donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1-3 R^d o R^e sustituyentes y el subíndice p es un número entero de 1 a 5. En una realización, p es 1. En otra realización, p es 2. En otra realización adicional, p es 5 y dos sustituyentes adyacentes de R^{12} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S; donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1-3 R^d o R^e sustituyentes y los otros tres R^{12} son, cada uno por separado, H, R^d o R^e. En algunas realizaciones, los dos sustituyentes adyacentes de R^{12} junto con los átomos a los cuales están unidos forman un anillo carbocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de benceno, ciclopentano, ciclohexano y benceno. Los sustituyentes en el anillo carbocíclico pueden ser de 1-2 grupos R^d o R^e. En otras realizaciones, dos sustituyentes adyacentes de R^{12} junto con los átomos a los cuales están unidos forman un anillo heterocíclico fusionado sustituido opcionalmente, incluyendo, no

taxativamente, anillos de pirrole, furano, tiofeno, pirazole, imidazole, oxazole, isoxazole, tiazole, isotiazole, piridina, piracina, piridazina, tetrahidrofurano, tetrahidropirano, tetrahidrotiofeno, pirazolidina, isoxazolidina, imidazolidina, oxazolidina, tiazolidina, isotiazolidina, piperidina, piperacina y hexahidropirimidina. Todas las otras variables Y^2, Q, R^4 y R^5 han sido definidas en cualquiera de las realizaciones descritas en este documento.

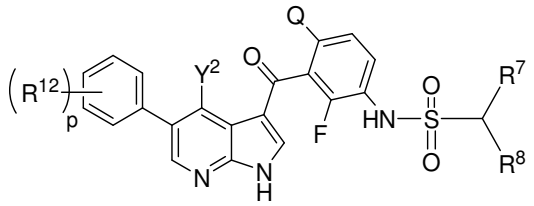
[0104] En una sexta realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Id-2):



Id-2

Todas las variables R^{12}, p, m, n y^2, Q y R^{11} han sido definidas en cualquiera de las realizaciones descritas en este documento. En algunas realizaciones, R^{11} es C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, heterocicloalquilo, heterocicloalquiloalquilo o R^e, el subíndice m es un número entero de 0 a 3 y el subíndice n es un número entero de 1 a 5.

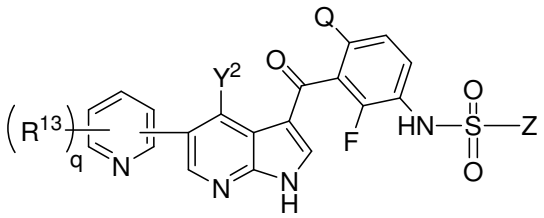
[0105] En una séptima realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Id-3):



Id-3

Todas las variables R^{12}, p y^2, Q, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento. En algunas realizaciones, R^7 y R^8 son cada uno por separado C_{1-6}alquilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo o $-X^2R^9$, donde la porción alifática o aromática de R^7 y R^8 es cada una sustituida opcionalmente con 1 a 3 miembros seleccionados por separado del grupo que consiste en C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo y R^e, proporcionado en cada aparición, como mínimo dos opciones cualesquiera de los grupos R^6, los grupos R^7 y R^8 no son simultáneamente hidrógeno; y donde X^2 es $-NR^{10}$, O o S; R^{10} es H, C_{1-6}alquilo o arilo; y R^9 es H, C_{1-6}alquilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo o heteroariloalquilo, donde R^9 es sustituido opcionalmente con 1 a 3 R^e sustituyentes.

[0106] En una octava realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Ie):

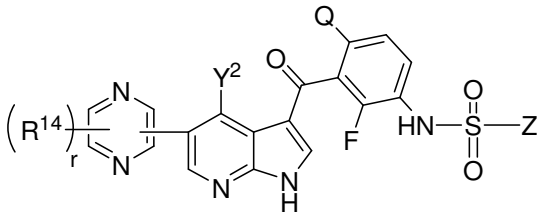


Ie

donde R^{13} es H o R^1; o dos grupos adyacentes R^{13} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S; y el subíndice q es un número entero de 1 a 4, donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1–3 sustituyentes R^d o R^e. En una realización, q es 1. En otra realización, q es 2. En otra realización adicional, q es 4 y dos sustituyentes adyacentes R^{13} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S; donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1–3 R^d o R^e sustituyentes y los otros dos grupos R^{13} son cada uno por separado H, R^d o R^e. En algunas realizaciones, los dos sustituyentes adyacentes R^{13} junto con los átomos a los cuales están unidos forman un anillo carbocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de benceno, ciclopentano y ciclohexano. Los sustituyentes en el anillo carbocíclico pueden ser de 1–2 grupos R^d o R^e. En otras realizaciones, dos grupos adyacentes R^{13} junto con los átomos a los cuales están unidos forman un anillo heterocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de pirrole,

furano, tiofeno, pirazole, imidazole, oxazole, isoxazole, tiazole, isotiazole, piridina, piracina, piridazina, tetrahidrofurano, tetrahidropirano, tetrahidrotiofeno, pirazolidina, isoxazolidina, imidazolidina, oxazolidina, tiazolidina, isotiazolidina, piperidina, piperacina y hexahidropirimidina. Todas las otras variables Y^2, Q y Z han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0107] En una novena realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (If):

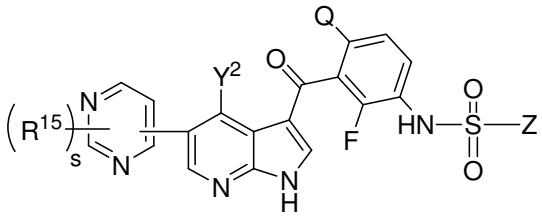


If

R^{14} es H o R^1; o dos grupos adyacentes R^{14} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S; y el subíndice r es un número entero de 1 a 3, donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1–3 sustituyentes R^d o R^e. En una realización, r es 1. En otra realización, r es 2. En otra realización adicional, r es 3 y dos sustituyentes adyacentes R^{14} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S; donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1–3 R^d o R^e sustituyentes y el otro R^{14} es H, R^d o R^e. En algunas rea-

lizaciones, los dos sustituyentes adyacentes R^{14} junto con los átomos a los cuales están unidos forman un anillo carbocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de benceno, ciclopentano y Ciclohexano. Los sustituyentes en el anillo carbocíclico pueden ser de 1-2 grupos R^d o R^e. En otras realizaciones, dos grupos sustituyentes adyacentes R^{14} junto con los átomos a los cuales están unidos forman un anillo heterocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de pirrole, furano, tiofeno, pirazole, imidazole, oxazole, isoxazole, tiazole, isotiazole, piridina, piracina, piridazina, tetrahidrofurano, tetrahidropirano, tetrahidrotiofeno, pirazolidina, isoxazolidina, imidazolidina, oxazolidina, tiazolidina, isotiazolidina, piperidina, piperacina y hexahidropirimidina. Todas las otras variables Y^2, Q y Z han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0108] En una décima realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Ig):



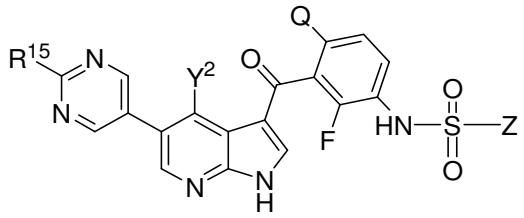
Ig

R^{15} es H o R^1; o dos grupos adyacentes R^{15} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de

O, N o S; y el subíndice s es un número entero de 1 a 3, donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1–3 sustituyentes R^d o R^e. En una realización, s es 1. En otra realización, s es 2. En otra realización adicional, s es 3 y dos sustituyentes adyacentes R^{15} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S; donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1–3 R^d o R^e sustituyentes y el otro R^{15} es H, R^d o R^e. En algunas realizaciones, los dos sustituyentes adyacentes R^{15} junto con los átomos a los cuales están unidos forman un anillo carbocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de benceno, ciclopentano y ciclohexano. Los sustituyentes en el anillo carbocíclico pueden ser 1–2 grupos R^d o R^e. En otras realizaciones, dos grupos sustituyentes adyacentes R^{15} junto con los átomos a los cuales están unidos forman un anillo heterocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de pirrole, furano, tiofeno, pirazole, imidazole, oxazole, isoxazole, tiazole, isotiazole, piridina, piracina, piridazina, tetrahidrofurano, tetrahidropirano, tetrahidrotiofeno, pirazolidina, isoxazolidina, imidazolidina, oxazolidina, tiazolidina, isotiazolidina, piperidina, piperacina y hexahidropirimidina. En otras realizaciones, R^{15} es halógeno, –CN, –OH, $-CF_3$, CF_3O-, C_{1-6}alquilo, C_{1-6}alcoxi, $-NO_2$, bencilo, fenilo, ciclopropilo, ciclopropilometilo, ciclobutilo, ciclobutilo–

metilo, ciclopentilo, ciclopentilometilo, ciclohexilo, ciclohexilmetilo, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ o $-NR^bR^b$. En algunas realizaciones, R^{15} es F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido o metilcarbamoilo, isopropilo, 1-pirrolidinilo, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo. Todas las otras variables Y^2, Q y Z han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0109] En una décimoprimera realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Ig-1):

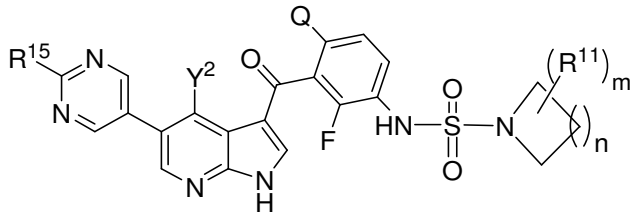


Ig-1

Todas las otras variables R^{15} y^2, Q y Z han sido definidas en cualquiera de las realizaciones descritas en este documento. En una realización preferida y^2 es H. En algunas realizaciones, R^{15} es H o R^1. En algunas realizaciones, R^{15} es R^a, R^b, R^c, R^d o R^e. En otras realizaciones, R^{15} es halógeno, –CN, –OH, $-CF_3$, CF_3O-, C_{1-6}alquilo, C_{1-6}alcoxi, $-NO_2$, bencilo, fenilo, ciclopropilo, ciclopropilometilo, ciclobutilo, ciclobutilometilo, ciclopentilo, ci-

clopentilometilo, ciclohexilo, cicloheximetilo, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ o $-NR^bR^b$. En algunas realizaciones, R^{15} es F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido o metilcarbamoilo, isopropilo, 1-pirrolidinilo, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo. En algunas realizaciones, Z es $-N(R^4)(R^5)$ o $-N(CH_3)(R^5)$. Todas las otras variables han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0110] En una decimosegunda realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Ig-2):



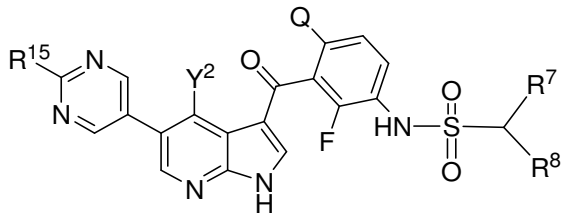
Ig-2

Todas las variables R^{15} y^2, Q, R^{11}, m y han sido definidas en cualquiera de las realizaciones descritas en este documento. En una realización preferida y^2 es H. En algunas realizaciones, R^{15} es H o R^1. En algunas realizaciones, R^{15} es R^a, R^b, R^c, R^d o R^e. En una realización, R^{15} es C_{1-6}alquilo. En otra realización, R^{15} es C_{3-6}cicloalquilo. En otra realización adicional, R^{15} es heterocicloalquilo. El subíndice m es un número entero de 0 a 3. El sub-

índice n es un número entero de 1 a 5. En algunas realizaciones, m es 0. En otras realizaciones, el subíndice n es 1, 2, 3 o 4. En algunas realizaciones, n es 1, 2 o 3 y m es 1 o 2. En algunas realizaciones, R^{11} es C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo o R^e. En algunas realizaciones, R^{11} es C_{1-6}alquilo, C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, heterocicloalquilo, heterocicloalquiloalquilo o R^e, cada uno de los cuales es sustituido opcionalmente con (i) 1–3 sustituyentes seleccionados por separado de C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, R^d o R^e; o (ii) 1, 2 o 3 sustituyentes R^a; o (iii) 1, 2 o 3 sustituyentes R^b; o (iv) 1, 2 o 3 sustituyentes R^c; o (v) 1, 2 o 3 sustituyentes R^d; o (vi) 1, 2 o 3 grupos R^f; el subíndice n es 1, 2, 3, 4 o 5 y el subíndice m es 0, 1, 2 o 3. En otras realizaciones, R^{11} es C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo o R^e. En algunas realizaciones, R^{11} es halógeno, C_{1-6}alquioxicarbonilo, C_{1-6}alquilo, C_{1-6}alquilo-(CO)NH- o C_{1-6}alquilo-(CO)(C_{1-6}alquilo)N-. En ciertas realizaciones, R^{11} es metoxicarbonilo, etoxicarbonilo, $-CH_3$, CH_3(CO)NH-, vinilo, propen-3-ilo o CH_3(CO)(CH_3)N-. En una realización de compuestos de fórmula Ig-2, el subíndice n es 1, m es 0 o 1. En otra realización de compues-

tos de fórmula Ig-2, el subíndice n es 2, m es 0, 1 o 2. En otra realización adicional, de compuestos de fórmula Ig-2, el subíndice n es 3, m es 0, 1 o 2. Todas las otras variables han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0111] En una decimotercera realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Ig-3):

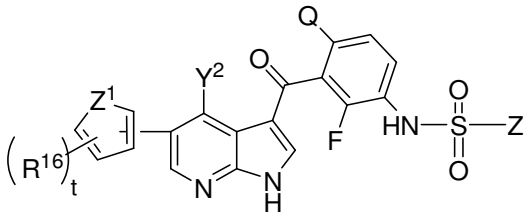


Ig-3

Todas las variables R^{15} y^2, Q, R^7 y R^8 han sido definidas en cualquiera de las realizaciones descritas en este documento. En una realización preferida y^2 es H. En algunas realizaciones, R^{15} es H o R^1. En algunas realizaciones, R^{15} es R^a, R^b, R^c, R^d o R^e. En una realización, R^{15} es C_{1-6}alquilo. En otra realización, R^{15} es C_{3-6}cicloalquilo. En otra realización adicional, R^{15} es heterocicloalquilo. En algunas realizaciones, R^7 y R^8 son cada uno por separado C_{1-6}alquilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo o $-X^2R^9$, donde la porción alifática o aromática de R^7 y R^8 es cada una sustituida opcionalmente con 1 a 3 miembros seleccionados por separado del grupo que consiste en C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo y R^e, proporcionado en cada apa-

rición, como mínimo dos opciones cualesquiera de los grupos R^6, los grupos R^7 y R^8 no son simultáneamente hidrógeno; y donde X^2 es $-NR^{10}$, O o S; R^{10} es H, C_{1-6}alquilo o arilo; y R^9 es H, C_{1-6}alquilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo o heteroariloalquilo, donde R^9 es sustituido opcionalmente con 1 a 3 sustituyentes R^e. En ciertos casos, $-C(R^7)(R^8)$ es un C_{3-6}alquilo ramificado. En una realización, $-C(R^7)(R^8)$ es isopropilo. En otra realización, $-C(R^7)(R^8)$ es sec-butilo. En otra realización adicional, $-C(R^7)(R^8)$ es pentan-2-ilo. En otra realización adicional, $-C(R^7)(R^8)$ es pentan-3-ilo. Todas las otras variables han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0112] En una decimocuarta realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Ih):



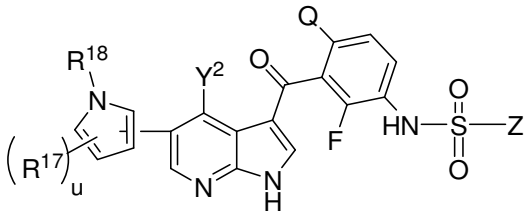
Ih

donde Z^1 es O o S; R^{16} es H o R^1; o dos grupos adyacentes R^{16} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S; donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1 a 3 R^d o R^e sustituyentes; y el subíndice t es un número entero de 1 a 3. En una realización, Z^1

es O. En otra realización, Z^1 es S. En una realización, t es 1. En otra realización, t es 2. En otra realización adicional, t es 3 y dos sustituyentes adyacentes R^{16} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S; donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1-3 R^d o R^e sustituyentes y el otro R^{16} es H, R^d o R^e. En algunas realizaciones, los dos sustituyentes adyacentes R^{16} junto con los átomos a los cuales están unidos forman un anillo carbocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de benceno, ciclopentano y ciclohexano. Los sustituyentes en el anillo carbocíclico pueden ser de 1-2 grupos R^d o R^e. En otras realizaciones, dos grupos sustituyentes adyacentes R^{16} junto con los átomos a los cuales están unidos forman un anillo heterocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de pirrole, furano, tiofeno, pirazole, imidazole, oxazole, isoxazole, tiazole, isotiazole, piridina, piracina, piridazina, tetrahidrofurano, tetrahidropirano, tetrahidrotiofeno, pirazolidina, isoxazolidina, imidazolidina, oxazolidina, tiazolidina, isotiazolidina, piperidina, piperacina y hexahidropirimidina. En otras realizaciones, R^{16} es halógeno, -CN, -OH, $-CF_3$, CF_3O-, C_{1-6}alquilo, C_{1-6}alcoxi, $-NO_2$, bencilo, fenilo, ciclopropilo, ciclopropilometilo, ciclobutilo, ciclobutilometilo, ciclopentilo, ciclopentilometilo, ciclohexilo, cicloheximetilo, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, -

$NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ o $-NR^bR^b$. En algunas realizaciones, R^{16} es F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, isopropilo, 1-pirrolidinilo, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo. Todas las otras variables Y^2, Q y Z han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0113] En una decimoquinta realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Ii):



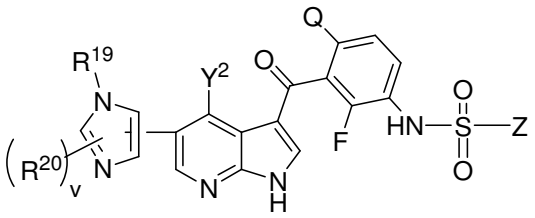
Ii

donde R^{18} es H, C_{1-6}alquilo, C_{1-6}haloalquilo, C_{3-6}cicloalquilo o C_{3-6}cicloalquilo. R^{17} es H o R^1; o dos grupos adyacentes R^{17} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S; o R^{17} y R^{18} tomados junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S, donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1 a 3 sustituyentes R^d o R^e; R^{18} es H, C_{1-6}alquilo

o C_{1-6}haloalquilo; y el subíndice u es un número entero de 1 a 3. En una realización, u es 1. En otra realización, u es 2. En otra realización adicional, u es 3 y dos sustituyentes adyacentes R^{17} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S; donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1–3 sustituyentes R^d o R^e y el otro R^{17} es H, R^d o R^e. En otras realizaciones, R^{17} y R^{18} tomados junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S, donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1 a 3 R^d o R^e sustituyentes. En algunas realizaciones, (i) los dos sustituyentes adyacentes R^{17} junto con los átomos a los cuales están unidos o (ii) R^{17} y R^{18} tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de benceno, ciclopentano y ciclohexano. Los sustituyentes en el anillo carbocíclico pueden ser de 1–2 grupos R^d o R^e. En otras realizaciones, (i) dos grupos sustituyentes adyacentes R^{17} junto con los átomos a los cuales están unidos o (ii) R^{17} y R^{18} tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de pirrole, furano, tiofeno, pirazole, imidazole, oxazole, isoxazole, tiazole, isotiazole, piridina,

piracina, piridazina, tetrahidrofurano, tetrahidropirano, tetrahidrotiofeno, pirazolidina, isoxazolidina, imidazolidina, oxazolidina, tiazolidina, isotiazolidina, piperidina, piperacina y hexahidropirimidina. En algunas realizaciones, R^{17} es halógeno, –CN, –OH, $–CF_3$, $CF_3O–$, C_{1-6}alquilo, C_{1-6}alcoxi, $–NO_2$, bencilo, fenilo, ciclopropilo, ciclopropilometilo, ciclobutilo, ciclobutilometilo, ciclopentilo, ciclopentilometilo, ciclohexilo, ciclohexilmetilo, $–OC(O)R^b$, $–C(O)R^b$, $–C(O)OR^b$, $–NHC(O)R^b$, $–C(O)NHR^b$, $–NHR^b$ o $–NR^bR^b$. En algunas realizaciones, R^{17} es F, Cl, Br, I, –CN, –OH, $–CF_3$, NH_2, $CF_3O–$, $CH_3–$, CH_3O, $–NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, isopropilo, 1-pirrolidinilo, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo. En ciertos casos, R^{18} es H, C_{1-6}alquilo o C_{1-6}haloalquilo. En algunas realizaciones, R^{18} es H, C_{1-6}alquilo o ciclopropilo, ciclopropilometilo, ciclobutilo, ciclobutilometilo, ciclopentilo, ciclopentilometilo, ciclohexilo, o ciclohexilometilo. En algunas realizaciones, R^{18} es H o CH_3. Todas las otras variables Y^2, Q y Z han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0114] En una decimosexta realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Ij):



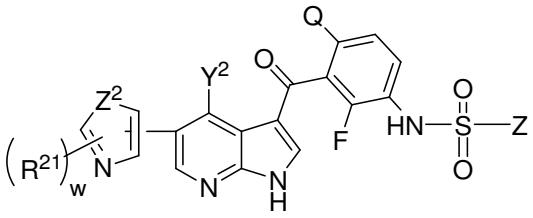
Ij

R^{19} es H, C_{1-6}alquilo, C_{1-6}haloalquilo, C_{3-6}cicloalquilo o C_{3-6}cicloalquilo. R^{20} es H o R^1; o dos grupos adyacentes R^{20} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S; o R^{20} y R^{19} tomados junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S; R^{19} es H, C_{1-6}alquilo o C_{1-6}haloalquilo; y el subíndice v es un número entero de 1 o 2, donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1 a 3 sustituyentes R^d o R^e. En una realización, v es 1. En algunas realizaciones, dos sustituyentes adyacentes R^{20} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S; donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1–3 sustituyentes R^d o R^e. En otras realizaciones, v es 2, R^{19} y R^{20} tomados junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene de 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S, donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1 a 3 sustituyentes R^d o R^e y el otro R^{20} es H, R^d o R^e . En algunas reali-

zaciones, (i) los dos sustituyentes adyacentes R^{20} junto con los átomos a los cuales están unidos o (ii) R^{19} y R^{20} tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de ciclopentano, ciclohexano y benceno. Los sustituyentes en el anillo carbocíclico pueden ser de 1-2 grupos R^{d} o R^{e}. En otras realizaciones, (i) dos grupos sustituyentes adyacentes R^{19} junto con los átomos a los cuales están unidos o (ii) R^{19} y R^{20} tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de pirrole, furano, tiofeno, pirazole, imidazole, oxazole, isoxazole, tiazole, isotiazole, piridina, piracina, piridazina, tetrahidrofurano, tetrahidropirano, tetrahidrotiofeno, pirazolidina, isoxazolidina, imidazolidina, oxazolidina, tiazolidina, isotiazolidina, piperidina, piperacina y hexahidropirimidina. En otras realizaciones, R^{20} es halógeno, -CN, -OH, $-CF_3$, CF_3O-, C_{1-6}alquilo, C_{1-6}alcoxi, $-NO_2$, bencilo, fenilo, ciclopropilo, ciclopropilometilo, ciclobutilo, ciclobutilometilo, ciclopentilo, ciclopentilometilo, ciclohexilo, cicloheximetilo, $-OC(O)R^{b}$, $-C(O)R^{b}$, $-C(O)OR^{b}$, $-NHC(O)R^{b}$, $-C(O)NHR^{b}$, $-NHR^{b}$ o $-NR^{b}R^{b}$. En algunas realizaciones, R^{20} es F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetami-

do, metilcarbamoilo, isopropilo, 1-pirrolidinilo, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo. En ciertos casos, R^{19} es H, C_{1-6}alquilo o C_{1-6}haloalquilo. En algunas realizaciones, R^{19} es H, C_{1-6}alquilo o ciclopropilo, ciclopropilometilo, ciclobutilo, ciclobutilometilo, ciclopentilo, ciclopentilometilo, ciclohexilo, o ciclohexilometilo. En algunas realizaciones, R^{19} es H o CH_3. Todas las otras variables Y^2, Q y Z han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0115] En una decimoséptima realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Ik):



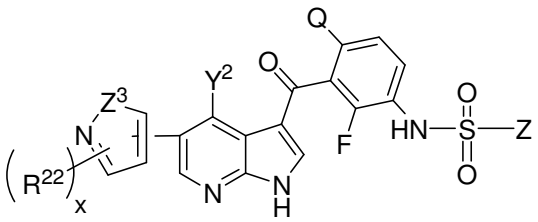
Ik

Z^2 es O o S. El subíndice w es 1 o 2. R^{21} es H o R^1; o dos grupos adyacentes R^{21} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S, donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1 a 3 sustituyentes R^d o R^e. En una realización, w es 1. En otra realización, w es 2. En algunas realizaciones, dos sustituyentes adyacentes R^{21} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como

miembros de anillo seleccionados de O, N o S; donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1-3 R^d o R^e sustituyentes. En algunas realizaciones, los dos sustituyentes adyacentes R^{21} junto con los átomos a los cuales están unidos forman un anillo carbocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de ciclopentano, ciclohexano y benceno. En ciertos casos, los sustituyentes en el anillo carbocíclico pueden ser de 1-2 grupos R^d o R^e. En otras realizaciones, dos grupos sustituyentes adyacentes R^{21} junto con los átomos a los cuales están unidos forman un anillo heterocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de pirrole, furano, tiofeno, pirazole, imidazole, oxazole, isoxazole, tiazole, isotiazole, piridina, piracina, piridazina, tetrahidrofurano, tetrahidropirano, tetrahidrotiofeno, pirazolidina, isoxazolidina, imidazolidina, oxazolidina, tiazolidina, isotiazolidina, piperidina, piperacina y hexahidropirimidina. En ciertos casos, los sustituyentes en el anillo heterocíclico pueden ser de 1-2 grupos R^d o R^e. En otras realizaciones, R^{21} es halógeno, -CN, -OH, $-CF_3$, CF_3O-, C_{1-6}alquilo, C_{1-6}alcoxi, $-NO_2$, bencilo, fenilo, ciclopropilo, ciclopropilometilo, ciclobutilo, ciclobutilometilo, ciclopentilo, ciclopentilometilo, ciclohexilo, cicloheximetilo, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ o $-NR^bR^b$. En algunas realizaciones, R^{21} es F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilo-

metiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, isopropilo, 1-pirrolidinilo, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo. Todas las otras variables Y^2, Q y Z han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0116] En una octavo décima realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Il):



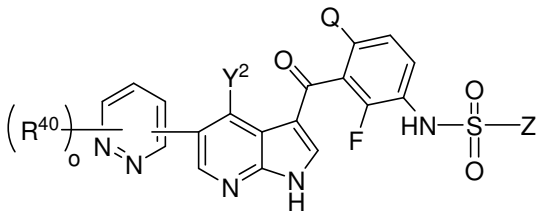
Il

Z^3 es O, S o $-N(R^{30})$, donde R^{30} es H, C_{1-6}alquilo, C_{1-6}haloalquilo, C_{3-6}cicloalquilo o C_{3-6}cicloalquilo. El subíndice x es 1 o 2. R^{22} es H o R^1; o dos grupos adyacentes R^{22} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S, donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1 a 3 sustituyentes R^d o R^e. En una realización, x es 1. En otra realización, x es 2. En algunas realizaciones, dos sustituyentes adyacentes R^{22} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S; donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1-3

sustituyentes R^d o R^e. En otras realizaciones, x es 2, R^{22} y R^{30} tomados junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene de 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S, donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1 a 3 R^d o R^e sustituyentes. En algunas realizaciones, (i) los dos sustituyentes adyacentes R^{22} junto con los átomos a los cuales están unidos o (ii) R^{22} y R^{30} tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de ciclopentano, ciclohexano y benceno. En ciertos casos, los sustituyentes en el anillo carbocíclico pueden ser de 1-2 grupos R^d o R^e. En otras realizaciones, (i) dos grupos sustituyentes adyacentes R^{22} junto con los átomos a los cuales están unidos o (ii) R^{22} y R^{30} tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de pirrole, furano, tiofeno, pirazole, imidazole, oxazole, isoxazole, tiazole, isotiazole, piridina, piracina, piridazina, tetrahidrofurano, tetrahidropirano, tetrahidrotiofeno, pirazolidina, isoxazolidina, imidazolidina, oxazolidina, tiazolidina, isotiazolidina, piperidina, piperacina y hexahidropirimidina. En otras realizaciones, R^{22} es halógeno, -CN, -OH, $-CF_3$, CF_3O-, C_{1-6}alquilo, C_{1-6}alcoxi, $-NO_2$, bencilo, fenilo, ciclopropilo, ciclopropilometilo, ciclobutilo, ciclobutilometilo, ciclopentilo, ciclopentilometilo, ciclohexi-

lo, cicloheximetilo, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ o $-NR^bR^b$. En algunas realizaciones, R^{22} es F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, isopropilo, 1-pirrolidinilo, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo. En ciertos casos, R^{30} es H, C_{1-6}alquilo o C_{1-6}haloalquilo. En algunas realizaciones, R^{30} es H, C_{1-6}alquilo o ciclopropilo, ciclopropilometilo, ciclobutilo, ciclobutilometilo, ciclopentilo, ciclopentilometilo, ciclohexilo, o ciclohexilometilo. En algunas realizaciones, R^{30} es H o CH_3. Todas las otras variables Y^2, Q y Z han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0117] En una noveno décima realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (Im):



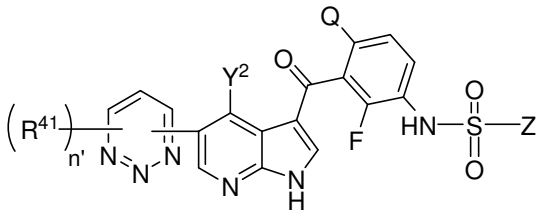
Im

R^{40} es H o R^1; o dos grupos adyacentes R^{40} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que

tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S; y el subíndice o es un número entero de 1 a 3, donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1–3 sustituyentes R^d o R^e. En una realización, el subíndice o es 1. En otra realización, el subíndice o es 2. En otra realización adicional, el subíndice o es 3 y dos sustituyentes adyacentes R^{40} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S; donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1–3 R^d o R^e sustituyentes y el otro R^{40} es H, R^d, R^e o R^f. En algunas realizaciones, los dos sustituyentes adyacentes R^{40} junto con los átomos a los cuales están unidos forman un anillo carbocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de benceno, ciclopentano y ciclohexano. Los sustituyentes en el anillo carbocíclico pueden ser de 1–2 grupos R^d o R^e. En otras realizaciones, dos grupos sustituyentes adyacentes R^{40} junto con los átomos a los cuales están unidos forman un anillo heterocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de pirrole, furano, tiofeno, pirazole, imidazole, oxazole, isoxazole, tiazole, isotiazole, piridina, piracina, piridazina, tetrahidrofurano, tetrahidropirano, tetrahidrotiofeno, pirazolidina, isoxazolidina, imidazolidina, oxazolidina, tiazolidina, isotiazolidina, piperidina, piperacina y hexahidropirimidina. En otras realizaciones, R^{40} es halógeno, –CN, –OH, $–CF_3$,

CF_3O–, C_{1-6}alquilo, C_{1-6}alcoxi, $-NO_2$, bencilo, fenilo, ciclopropilo, ciclopropilometilo, ciclobutilo, ciclobutilometilo, ciclopentilo, ciclopentilometilo, ciclohexilo, cicloheximetilo, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ o $-NR^bR^b$. En algunas realizaciones, R^{40} es F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O–, CH_3–, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1–cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido o metilcarbamoilo, isopropilo, 1–pirrolidinilo, 1–ciclopropiloetilo, 2–ciclopropiloetilo, 1–ciclopropiloetilamino, 2–ciclopropiloetilamino o 1–hidroxi–1–metiletilo. Todas las otras variables Y^2, Q y Z han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0118] En una vigésima realización de la invención, los compuestos de fórmula (I) tienen la subfórmula (In):



In

R^{41} es H o R^1; o dos grupos adyacentes R^{41} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S; y el subíndice n’ es un número entero de 1 o 2, donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1–3

sustituyentes R^d o R^e. En una realización, el subíndice n' es 1. En otra realización, el subíndice n' es 2. En algunas realizaciones, los dos sustituyentes adyacentes R^{41} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S; donde el anillo de 5 a 6 miembros es sustituido opcionalmente con 1-3 sustituyentes R^d o R^e. En algunas realizaciones, los dos sustituyentes adyacentes R^{41} junto con los átomos a los cuales están unidos forman un anillo carbocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de benceno, ciclopentano y Ciclohexano. Los sustituyentes en el anillo carbocíclico pueden ser de 1-2 grupos R^d o R^e. En otras realizaciones, dos sustituyentes adyacentes R^{41} grupos junto con los átomos a los cuales están unidos forman un anillo heterocíclico fusionado sustituido opcionalmente, incluyendo, no taxativamente, anillos de pirrole, furano, tiofeno, pirazole, imidazole, oxazole, isoxazole, tiazole, isotiazole, piridina, piracina, piridazina, tetrahidrofurano, tetrahidropirano, tetrahidrotiofeno, pirazolidina, , isoxazolidina, imidazolidina, oxazolidina, tiazolidina, isotiazolidina, piperidina, piperacina y hexahidropirimidina. En otras realizaciones, R^{41} es halógeno, -CN, -OH, $-CF_3$, CF_3O-, C_{1-6}alquilo, C_{1-6}alcoxi, $-NO_2$, bencilo, fenilo, ciclopropilo, ciclopropilometilo, ciclobutilo, ciclobutilometilo, ciclopentilo, ciclopentilometilo, ciclohexilo, cicloheximetilo, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ o $-NR^bR^b$.

En algunas realizaciones, R^{41} es F, Cl, Br, I, –CN, –OH, $–CF_3$, NH_2, $CF_3O–$, $CH_3–$, CH_3O, $–NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido o metilcarbamoilo, isopropilo, 1-pirrolidinilo, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo. Todas las otras variables Y^2, Q y Z han sido definidas en cualquiera de las realizaciones descritas en este documento.

[0119] En algunas realizaciones, la invención proporciona un compuesto seleccionado del grupo que consiste en:

N-[3-[5-(4-clorofenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0012);**

5-cloro-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0013);**

5-(4-clorofenilo)-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0014);**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0015);**

N-[2,4-difluoro-3-(5-fluoro-4-yodo-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]pirrolodina-1-sulfonamida **(P-0016);**

N-[3-[4-(ciclopropilometiloamino)-5-fluoro-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0017);**

5-ciano-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0018);**

5-cloro-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0019);**

5-(4-clorofenilo)-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0020);**

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0021);**

N-[3-[5-(4-clorofenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0022);**

N-[3-[5-[2-(dimetilamino)pirimidin-5-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0023);**

N-[2-fluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]pirrolodina-1-sulfonamida **(P-0024);**

N-[2,4-difluoro-3-(5-yodo-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]pirrolodina-1-sulfonamida **(P-0025);**

3-[3-[[ciclopropilo(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0026);**

[2-fluoro-3-(metilsulfamoilamino)fenilo]-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridin-3-il]metanona **(P-0027);**

5-(4-cianofenilo)-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0028);**

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-(3-piridilo)-1H-pirrolo[2,3-b]piridina **(P-0029);**

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-(6-metil-3-piridilo)-1H-pirrolo[2,3-b]piridina **(P-0030);**

5-[6-(dimetilamino)-3-piridilo]-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0031);**

5-(4-cianofenilo)-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0032);**

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(3-piridilo)-1H-pirrolo[2,3-b]piridina **(P-0033);**

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(6-metil-3-piridilo)-1H-pirrolo[2,3-b]piridina **(P-0034);**

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(4-fluorofenilo)-1H-pirrolo[2,3-b]piridina **(P-0035);**

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-(4-fluorofenilo)-1H-pirrolo[2,3-b]piridina;

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-fenilo-1H-pirrolo[2,3-b]piridina **(P-0036);**

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-fenilo-1H-pirrolo[2,3-b]piridina **(P-0037);**

5-bromo-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0038);**

5-ciano-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0039);**

3-[2-fluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0040);**

3-benciloxi-N-[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0041);**

1-ciclopropilo-N-[2-fluoro-3-[5-(1-metilpirazol-4-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]metanosulfonamida **(P-0042);**

N-[2-fluoro-3-[5-(3-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0043);**

N-[3-[5-(2,4-dimetoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0044);**

N-[2-fluoro-3-[5-(6-metil-3-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0045);**

N-[3-[5-[6-(dimetilamino)-3-piridilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0046);**

N-[2-fluoro-3-[5-(2-isopropilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0047);**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0048);**

N-[3-[5-(4-ciano-3-metoxi-fenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0049);**

N-[3-[5-[4-(1-cianociclopropilo)fenilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0050);**

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-(2-isopropilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0051);**

5-(2-ciclopropilopirimidin-5-il)-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0052);**

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-[6-(trifluorometil)-3-piridilo]-1H-pirrolo[2,3-b]piridina **(P-0053);**

5-(4-ciano-3-metoxi-fenilo)-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0054);**

5-[4-(1-cianociclopropilo)fenilo]-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0055);**

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-metilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0056);**

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-isopropilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0057);**

5-(2-ciclopropilopirimidin-5-il)-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0058);**

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-[6-(trifluorometil)-3-piridilo]-1H-pirrolo[2,3-b]piridina **(P-0059);**

5-(4-ciano-3-metoxi-fenilo)-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0060);**

5-[4-(1-cianociclopropilo)fenilo]-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0061);**

N-[2-fluoro-3-[5-(4-fluorofenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0062);**

N-[2-fluoro-3-(5-fenilo-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]pirrolodina-1-sulfonamida **(P-0063);**

5-[2-(ciclopropiloamino)pirimidin-5-il]-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0064);**

N-[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]-2-metoxi-etanosulfonamida **(P-0065);**

metil 3-[[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]sulfamoil]propanoato **(P-0066);**

N-[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]ciclopropanosulfonamida **(P-0067);**

[3-(etilsulfamoilamino)-2-fluoro-fenilo]-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridin-3-il]metanona **(P-0068);**

[3-(etilsulfamoilamino)-2-fluoro-fenilo]-(5-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona **(P-0069);**

3-[2-fluoro-3-[[isobutil(metil)sulfamoil]amino]benzoil]-5-yodo-1H-pirrolo[2,3-b]piridina **(P-0070);**

[2-fluoro-3-(isopropilsulfamoilamino)fenilo]-(5-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona **(P-0071);**

3-[2-fluoro-3-[[isobutil(metil)sulfamoil]amino]benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0072);**

3-[2-fluoro-3-[[2-metoxietil(metil)sulfamoil]amino]benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0073);**

N-[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]-2-metil-pirrolodina-1-sulfonamida **(P-0074);**

3-[2-fluoro-3-[[isopropil(metil)sulfamoil]amino]benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0075);**

5-[6-(dimetilamino)-3-piridilo]-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0076);**

5-[2-(ciclopropiloamino)pirimidin-5-il]-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0077);**

5-(2-ciclopropilopirimidin-5-il)-3-[2,6-difluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina **(P-0078);**

5-[4-(1-cianociclopropilo)fenilo]-3-[2,6-difluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina **(P-0079);**

5-[4-(1-cianociclopropilo)fenilo]-3-[2-fluoro-3-[[2-metoxietil(metil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina **(P-0080);**

5-[2-(ciclopropiloamino)pirimidin-5-il]-3-[2-fluoro-3-[[2-metoxietil(metil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina **(P-0081);**

5-[2-(ciclopropiloamino)pirimidin-5-il]-3-[2-fluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina **(P-0082);**

3-[3-[[ciclopropilometilo(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0083);**

3-[3-[[ciclopropilometilo(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0084);**

5-(2-ciclopropilopirimidin-5-il)-3-[2-fluoro-3-[[2-metoxietil(metil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina **(P-0085);**

5-(2-ciclopropilopirimidin-5-il)-3-[2-fluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina **(P-0086);**

5-(6-ciclopropilo-3-piridilo)-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0087);**

3,3-difluoro-N-[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]acetidina-1-sulfonamida **(P-0088);**

4-[[(1S)-1-ciclopropiloetil]amino]-5-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-7H-pirrolo[2,3-d]pirimidina **(P-0089);**

N-[3-[5-(4-cianofenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0090);**

N-[3-[5-(2-cianopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0091);**

N-[2-fluoro-3-[5-(2-metilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0092);**

N-[3-[5-(5-ciano-3-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0093);**

N-[2-fluoro-3-[5-[6-(trifluorometil)-3-piridilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0095);**

5-(2-cianopirimidin-5-il)-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0096);**

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-(2-metilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0097);**

5-(5-ciano-3-piridilo)-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0098);**

5-(6-ciano-3-piridilo)-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0099);**

5-(2-cianopirimidin-5-il)-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0100);**

5-(5-ciano-3-piridilo)-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0101);**

5-(6-ciano-3-piridilo)-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0102);**

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-[4-(1-hidroxi-1-metil-etil)fenilo]-1H-pirrolo[2,3-b]piridina **(P-0103);**

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-[4-(1-hidroxi-1-metil-etil)fenilo]-1H-pirrolo[2,3-b]piridina **(P-0104);**

N-[2-fluoro-3-[5-[4-(1-hidroxi-1-metil-etil)fenilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0105);**

5-[2-(dimetilamino)pirimidin-5-il]-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0106);**

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-(2-pirrolidin-1-ilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0107);**

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-pirrolidin-1-ilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0108);**

N-[2-fluoro-3-[5-(2-pirrolidin-1-ilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0109);**

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-yodo-1H-pirrolo[2,3-b]piridina **(P-0110);**

3-[2-fluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-5-(2-metilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0111);**

3-[3-[[ciclopropilometilo(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-metilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0112);**

5-(6-ciclopropilo-3-piridilo)-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0113);**

5-(6-ciclopropilo-3-piridilo)-3-[2-fluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina **(P-0114);**

3-[3-[[ciclopropilometilo(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(6-ciclopropilo-3-piridilo)-1H-pirrolo[2,3-b]piridina **(P-0115);**

3-[2,6-difluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0116);**

[2-fluoro-3-(propilsulfamoilamino)fenilo]-(5-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona **(P-0117);**

[2-fluoro-3-(propilsulfamoilamino)fenilo]-(5-metil-1H-pirrolo[2,3-b]piridin-3-il)metanona **(P-0223);**

N-[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]butano-2-sulfonamida **(P-0024);**

N-[2-fluoro-3-[5-(2-pirrolidin-1-ilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]butano-2-sulfonamida **(P-0225);**

N-[3-[5-[2-(ciclopropiloamino)pirimidin-5-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]butano-2-sulfonamida **(P-0226);**

N-[3-[5-[4-(1-cianociclopropilo)fenilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]butano-2-sulfonamida **(P-00227);**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]butano-2-sulfonamida **(P-0228);**

N-[2-fluoro-3-[5-(2-isopropilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]butano-2-sulfonamida **(P-0229);**

N-[3-[5-[6-(dimetilamino)-3-piridilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]butano-2-sulfonamida **(P-0230);**

N-[2-fluoro-3-[5-(2-metilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]butano-2-sulfonamida **(P-0231);**

N-[3-[5-[2-(ciclopropiloamino)pirimidin-5-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0232);**

5-(2-ciclopropilopirimidin-5-il)-3-[2-fluoro-3-[[isopropil(metil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina **(P-0233);**

N-[2-fluoro-3-[5-(2-morfolinopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida; (**P-0235**);

N-[2-fluoro-3-[5-(2-morfolinopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]butano-2-sulfonamida (**P-0236**);

5-[4-(1-cianociclopropilo)fenilo]-3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0237);**

5-(2-ciclopropilopirimidin-5-il)-3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0238);**

5-[4-(1-cianociclopropilo)fenilo]-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0239);**

5-(2-ciclopropilopirimidin-5-il)-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0240);**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0241);**

[2-fluoro-3-(propilsulfamoilamino)fenilo]-[5-(1-metilpirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-il]metanona **(P-0242);**

1-[4-[3-[2-fluoro-3-(pirrolidin-1-ilsulfonilamino)benzoil]-1H-

pirrolo[2,3-b]piridin-5-il]fenilo]ciclopropano ácido carboxílico **(P-0243);**

3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-5-(5-etoxipiracin-2-il)-1H-pirrolo[2,3-b]piridina **(P-0244);**

5-[4-(1-ciano-1-metil-etil)fenilo]-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0245);**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]-3,3-dimetil-pirrolodina-1-sulfonamida **(P-0246);**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]-3-metil-pirrolodina-1-sulfonamida **(P-0247);**

N-[3-[5-[4-(1-cianociclopropilo)fenilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0248);**

3-[3-[[ciclopropilo(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0249);**

[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridin-3-il]-[2-fluoro-3-(propilsulfamoilamino)fenilo]metanona **(P-0251);**

3-[3-[[ciclopropilo(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-

b]piridina **(P-0252);**

1-[4-[3-[2-fluoro-3-(pirrolidin-1-ilsulfonilamino)benzoil]-1H-pirrolo[2,3-b]piridin-5-il]fenilo]ciclopropanocarboxamida **(P-0253);**

metil 1-[4-[3-[2-fluoro-3-(pirrolidin-1-ilsulfonilamino)benzoil]-1H-pirrolo[2,3-b]piridin-5-il]fenilo]ciclopropanocarboxilato **(P-0254);**

5-[4-(1-ciano-1-metil-etil)fenilo]-3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0255);**

5-(2-etoxipirimidin-5-il)-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0256);**

etil 1-[[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]sulfamoil]pirrolodina-2-carboxilato **(P-0257);**

4-[5-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]pirimidin-2-il]morfolina **(P-0258);**

4-[3-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]fenilo]morfolina **(P-0259);**

N-[2,4-difluoro-3-[5-[2-(4-metilpiperacin-1-il)pirimidin-5-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0260);**

N-[2,4-difluoro-3-[5-(2-piperacin-1-ilpirimidin-5-il)-1H-

pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0261);**

N-[2,4-difluoro-3-[5-[2-(4-hidroxi-1-piperidil)pirimidin-5-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0262);**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-[2-(4-metilpiperacin-1-il)pirimidin-5-il]-1H-pirrolo[2,3-b]piridina **(P-0263);**

terc-butil 4-[5-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]pirimidin-2-il]piperacina-1-carboxilato **(P-0264);**

N-[2,4-difluoro-3-[5-[2-(1-hidroxi-1-metil-etil)tiazol-4-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0265);**

N-[2,4-difluoro-3-[5-(2-morfolinopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0266);**

N-[1-[[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]sulfamoil]pirrolidin-3-il]-N-metil-acetamida **(P-0267);**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(2-piperacin-1-ilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0268);**

N-[3-[5-[2-(azetidin-1-il)pirimidin-5-il]-1H-pirrolo[2,3-

b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0269);**

N-[2,4-difluoro-3-[5-(2-metoxitiazol-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0270);**

(3R)-N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]-3-metil-pirrolodina-1-sulfonamida **(P-0271);**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]-3-(metilamino)pirrolodina-1-sulfonamida **(P-0272);**

N-[2,4-difluoro-3-[5-(4-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0273);**

N-[3-(5-ciclopropilo-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0274);**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-[2-(4-hidroxi-1-piperidil)pirimidin-5-il]-1H-pirrolo[2,3-b]piridina **(P-0275);**

5-[3-(1-cianociclopropilo)fenilo]-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0276);**

5-[2-(azetidin-1-il)pirimidin-5-il]-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0277);**

N-[3-[5-(2-aminopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0279);**

N-[3-[5-(2-aminopirimidin-4-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0280);**

N-[2-fluoro-3-[5-(4-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0281);**

N-[2,4-difluoro-3-[5-(2-morfolinopirimidin-4-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0282);**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(2-fluoro-4-piridilo)-1H-pirrolo[2,3-b]piridina **(P-0283);**

N-[2,4-difluoro-3-[5-(2-morfolino-4-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0284);**

N-[2,4-difluoro-3-[5-[2-(4-metilpiperacin-1-il)-4-piridilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0285);**

N-[3-[5-[2-(ciclobutoxi)-4-piridilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0286);**

N-[2,4-difluoro-3-[5-(2-metoxi-4-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-**

0287);

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]-3,3-difluoro-pirrolodina-1-sulfonamida **(P-0288);**

(3S)-N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]-3-fluoro-pirrolodina-1-sulfonamida **(P-0289);**

metil 2-[[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]sulfamoil]propanoato **(P-0291);**

5-[2-(dimetilamino)pirimidin-5-il]-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0292);**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(2-pirrolidin-1-ilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0293);**

N-[2,4-difluoro-3-[5-[6-(trifluorometil)pirimidin-4-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0294);**

N-[3-[5-(2-ciclopropilo-4-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0295);**

5-ciclobutilo-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0297);**

5-ciclopropilo-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0298);**

N-[3-[5-(6-aminopirimidin-4-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0299);**

5-(4-cianofenilo)-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0300);**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-[4-(trifluorometil)fenilo]-1H-pirrolo[2,3-b]piridina **(P-0301);**

5-[3-(dimetilamino)fenilo]-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0302);**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(4-pirrolidin-1-ilfenilo)-1H-pirrolo[2,3-b]piridina **(P-0303);**

2-[4-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]fenilo]-5-metil-1,3,4-oxadiazole **(P-0304);**

2-[4-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]fenilo]-5-(metilamino)-1,3,4-tiadiazole **(P-0305);**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-[5-(1-hidroxi-1-metil-etil)-3-piridilo]-1H-pirrolo[2,3-b]piridina **(P-0306);**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-[6-(1-hidroxi-1-metil-etil)-3-piridilo]-1H-pirrolo[2,3-b]piridina **(P-0307);**

5-[4-(dietilamino)fenilo]-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0308);**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(2-oxoindolin-6-il)-1H-pirrolo[2,3-b]piridina **(P-0309);**

3-[5-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]-2-tienilo]-5-metil-1,2,4-oxadiazole **(P-0310);**

2-amino-6-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]quinazolina **(P-0311);**

N-ciclopropilo-5-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]piridina-2-carboxamida **(P-0312);**

2-(dimetilamino)-6-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]quinazolina **(P-0313);**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-[4-(1-hidroxiciclopropilo)fenilo]-1H-pirrolo[2,3-b]piridina **(P-0314);**

5-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]tiazole **(P-0315);**

4-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]-2-(1-hidroxi-1-metil-etil)tiazole **(P-0316);**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(6-

metoxipiridazin-3-il)-1H-pirrolo[2,3-b]piridina **(P-0317);**

N-[2,4-difluoro-3-[5-(6-morfolinopirimidin-4-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0318);**

N-[2,4-difluoro-3-[5-[6-(4-metilpiperacin-1-il)pirimidin-4-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0319);**

(3S)-N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]-3-metil-pirrolodina-1-sulfonamida **(P-0320);**

N-[2-fluoro-3-[5-(6-morfolinopirimidin-4-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0321);**

N-[2-fluoro-3-[5-[6-(4-metilpiperacin-1-il)pirimidin-4-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0322);**

N-[2-fluoro-3-[5-[6-(4-metilpiperacin-1-il)-2-piridilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0324);**

N-[2-fluoro-3-[5-(4-metoxipirimidin-2-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0325);**

N-[2-fluoro-3-[5-(4-metilpirimidin-2-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-**

0326);

(3R)-N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]-3-fluoro-pirrolodina-1-sulfonamida **(P-0327);**

[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridin-3-il]-[2,6-difluoro-3-(metilsulfamoilamino)fenilo]metanona **(P-0334);**

[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridin-3-il]-[3-(etilsulfamoilamino)-2,6-difluoro-fenilo]metanona **(P-0335);**

5-(2-ciclopropilopirimidin-5-il)-3-[2,6-difluoro-3-(sulfamoilamino)benzoil]-1H-pirrolo[2,3-b]piridina **(P-0336);**

N-[3-[5-(4-clorofenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]butano-2-sulfonamida **(P-0337);**

(3R)-N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]-3-fluoro-pirrolodina-1-sulfonamida **(P-0338);**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]-3-fluoro-pirrolodina-1-sulfonamida **(P-0339);**

5-(2-ciclopropilopirimidin-5-il)-3-[2,6-difluoro-3-[[metil(2,2,2-trifluoroetil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina **(P-0340);**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-

b]piridina-3-carbonilo]-2,4-difluoro-fenilo]butano-2-sulfonamida **(P-0342);**

5-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]-2-metoxi-tiazole **(P-0343);**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(1H-indazol-6-il)-1H-pirrolo[2,3-b]piridina **(P-0344);**

N-[2,4-difluoro-3-[5-(2-pirrolidin-1-ilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0345);**

N-[3-(5-ciclobutilo-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0346);**

N-[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]ciclopropanosulfonamida **(P-0347);**

1-allilo-N-[3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]ciclopropanosulfonamida **(P-0348);**

N-[2,4-difluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]ciclopropanosulfonamida **(P-0349);**

N-[2,4-difluoro-3-[5-(5-metoxi-3-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]ciclopropanosulfonamida **(P-0350);**

y

N-[3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]ciclopropanosulfonamida **(P-0351);**

o sales, hidratos, solvatos, tautómeros o isómeros de los mismos aceptables farmacéuticamente. En algunas realizaciones, la invención proporciona los compuestos seleccionados anteriormente y

sales de los mismos aceptables farmacéuticamente. En otras realizaciones, la invención proporciona los compuestos seleccionados anteriormente y sales y tautómeros e isómeros de los mismos aceptables farmacéuticamente.

[0120] En otras realizaciones, la invención proporciona un compuesto seleccionado de cualquiera de P-0108 a P-0222 según se establece en Tabla 3 y sales, hidratos, solvatos, tautómeros e isómeros de los mismos aceptables farmacéuticamente. En algunas realizaciones, la invención proporciona cualquiera de los compuestos seleccionados anteriormente y sales de los mismos aceptables farmacéuticamente. En algunas realizaciones, la invención proporciona cualquiera de los compuestos seleccionados anteriormente y sales y tautómeros e isómeros de los mismos aceptables farmacéuticamente.

[0121] En algunas realizaciones, cuando Y^1 es sustituido opcionalmente 2-piridilo, 3-piridilo o 4-piridilo, Z es otro aparte de $-N(CH_3)(CH_3)$ o $-N(R^4)_2$, donde R^4 es C_{1-6}alquilo. En algunas realizaciones, cuando Y^1 es fenilo, Z es otro aparte de $-N(CH_3)(CH_3)$ o $-N(R^4)_2$, donde R^4 es C_{1-6}alquilo. En otras realizaciones, cuando Y^1 es halógeno, Z es otro aparte de $-N(CH_3)(CH_3)$, $-N(Et)_2$, 1-pirrolinilo, 1-piperidinilo, 4-morfolinilo o $-N(R^4)_2$, donde R^4 es C_{1-6}alquilo. En algunas realizaciones, cuando Y^1 es CH_3 o C_{1-6}alquilo, Z es otro aparte de $-N(CH_3)(CH_3)$, $-N(Et)_2$, 1-pirrolinilo, 1-piperridinilo, 4-morfolinilo o $-N(R^4)_2$, donde R^4 es C_{1-6}alquilo. En algunas realizaciones, cuando Y^1 es CH_3O- o C_{1-}

$_6$alcoxi, Z es otro aparte de $-N(CH_3)(CH_3)$, $-N(Et)_2$, 1-pirrolinilo, 1-piperridinilo, 4-morfolinilo o $-N(R^4)_2$, donde R^4 es C_{1-6}alquilo. En algunas realizaciones, cuando Y^1 es CN, Z es otro aparte de $-N(CH_3)(CH_3)$, $-N(Et)_2$, 1-pirrolinilo, 1-piperridinilo, 4-morfolinilo o $-N(R^4)_2$, donde R^4 es C_{1-6}alquilo. En ciertos casos, cuando Y^1 es halógeno, $-CH_3$, -CN, -OMe o 2-metoxipirimidin-5-il, Z es otro aparte de C_{3-6}cicloalquilo. En otros casos, cuando Y^1 es 1-metil-4-pirazolilo, 3-metilsulfonilfenilo o 3-metilsulfonilaminofenilo, Z es otro aparte de C_{3-6}cicloalquilo. En otros casos, cuando Y^1 es C_{1-6}alquilo o C_{1-6}alcoxi, Z es otro aparte de C_{3-6}cicloalquilo. En otros casos, cuando Y^1 es 1-C_{1-6}alquilo-4-pirazolilo, Z es otro aparte de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo. En otros casos, cuando Y^1 es 1-C_{1-6}alquilo-4-pirazolilo, Z es otro aparte de C_{3-6}cicloalquilo. En otros casos, cuando Y^1 es metilsulfonilfenilo o metilsulfonilaminofenilo, Z es otro aparte de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo. En otros casos, cuando Y^1 es metilsulfonilfenilo o metilsulfonilaminofenilo, Z es otro aparte de C_{3-6}cicloalquilo. En algunos casos, cuando Y^1 es 3-C_{1-6}alquilosulfonilfenilo o 3-C_{1-6}alquilosulfonilaminofenilo, Z es otro aparte de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo. En otros casos, cuando Y^1 es 3-C_{1-6}alquilosulfonilfenilo o 3-C_{1-6}alquilosulfonilaminofenilo, Z es otro aparte de C_{3-6}cicloalquilo.

[0122] Los compuestos siguientes en la Tabla 1 están excluidos de las fórmulas genéricas I y Ia a In:

Tabla 1

3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-5-(3-piridilo)-1H-pirrolo[2,3-b]piridina;

5-bromo-3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina;

3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-5-fenilo-1H-pirrolo[2,3-b]piridina;

N-[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]piperidina-1-sulfonamida;

5-(4-clorofenilo)-3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina;

5-cloro-3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina;

(5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-[3-[dimetilsulfamoil(metil)amino]-2,6-difluoro-fenilo]metanona;

N-[2,4-difluoro-3-(5-metoxi-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]pirrolodina-1-sulfonamida;

N-[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida;

N-[2,4-difluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]pirrolodina-1-sulfonamida;

N-[3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida;

5-ciano-3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina;

3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-5-metil-1H-pirrolo[2,3-b]piridina;

5-cloro-3-[3-(dietilsulfamoilamino)-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina;

5-ciano-3-[3-(dietilsulfamoilamino)-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina;

3-[3-(dietilsulfamoilamino)-2,6-difluoro-benzoil]-5-metil-1H-pirrolo[2,3-b]piridina;

3-[3-(dietilsulfamoilamino)-2,6-difluoro-benzoil]-5-metoxi-1H-pirrolo[2,3-b]piridina;

N-[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]morfolina-4-sulfonamida;

N-[2,4-difluoro-3-(5-metoxi-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]morfolina-4-sulfonamida;

N-[2,4-difluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]morfolina-4-sulfonamida;

N-[3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]morfolina-4-sulfonamida;

3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina;

N-[2,4-difluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida;

3-[3-(dietilsulfamoilamino)-2,6-difluoro-benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina;

N-[2,4-difluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]morfolina-4-sulfonamida;

5-ciano-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina;

N-[3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-fenilo]pirrolodina-1-sulfonamida;

N-[3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-fenilo]morfolina-4-sulfonamida;

N-[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida;

5-(4-clorofenilo)-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina;

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina;

Ácido propano-2-sulfónico[2,4-difluoro-3-(5-metoxi-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido pirrolodina-1-sulfónico [2,4-difluoro-3-(5-metoxi-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido propano-2-sulfónico[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido propano-2-sulfónico[3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido propano-2-sulfónico{2,4-difluoro-3-[5-(2-metoxi-pirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-fenilo}-amida;

Ácido butano-2-sulfónico [2,4-difluoro-3-(5-metoxi-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido pentano-2-sulfónico [2,4-difluoro-3-(5-metoxi-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido butano-2-sulfonico [3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido pentano-2-sulfónico [3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido butano-2-sulfonico [2,4-difluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido pentano-2-sulfónico [3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido pentano-2-sulfónico [2,4-difluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido butano-2-sulfonico [3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido butano-2-sulfonico {2,4-difluoro-3-[5-(2-metoxi-pirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-fenilo}-amida;

Ácido ciclobutanosulfónico[3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido ciclobutanosulfónico[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido ciclohexanosulfónico [2,4-difluoro-3-(5-metoxi-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido ciclopentanosulfónico [2,4-difluoro-3-(5-metoxi-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido ciclohexanosulfónico [3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido ciclopentanosulfónico [3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido ciclopentanosulfónico [3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido ciclohexanosulfónico [2,4-difluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido ciclobutanosulfónico[2,4-difluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido ciclopentanosulfónico [2,4-difluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido ciclohexanosulfónico [3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido ciclohexanosulfónico {2,4-difluoro-3-[5-(2-metoxi-pirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-fenilo}-amida;

Ácido ciclopentanosulfónico {2,4-difluoro-3-[5-(2-metoxi-pirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-fenilo}-amida;

Ácido ciclobutanosulfónico{2,4-difluoro-3-[5-(2-metoxi-pirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-fenilo}-amida;

Ácido pirrolodina-1-sulfónico [2,4-difluoro-3-(5-metoxi-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido pirrolodina-1-sulfónico [3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido pirrolodina-1-sulfónico [2,4-difluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido pirrolodina-1-sulfónico [2,4-difluoro-3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido N,N-dimetilamino-sulfónico [2,4-difluoro-3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido N,N-dimetilamino-sulfónico [2,4-difluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido N,N-dietilamino-sulfónico [3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido N,N-dietilamino-sulfónico [3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido N,N-dietilamino-sulfónico [2,4-difluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido N,N-dietilamino-sulfónico [2,4-difluoro-3-(5-metoxi-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido morfolina-4-sulfónico[3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido morfolina-4-sulfónico[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida;

Ácido morfolina-4-sulfónico[2,4-difluoro-3-(5-metoxi-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido morfolina-4-sulfónico[2,4-difluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido propano-2-sulfónico[3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-fenilo]-amida;

Ácido butano-2-sulfónico [3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-fenilo]-amida;

Ácido ciclohexanosulfónico [3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-fenilo]-amida;

Ácido ciclopentanosulfónico [3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-fenilo]-amida;

Ácido ciclobutanosulfónico[3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-fenilo]-amida;

Ácido ciclopropanosulfónico {4-fluoro-3-[5-(1-metil-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-fenilo}-amida;

Ácido ciclohexanosulfónico {4-fluoro-3-[5-(1-metil-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-fenilo}-amida;

Ácido ciclopropanosulfónico [3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-4-fluoro-fenilo]-amida;

Ácido ciclohexanosulfónico [4-fluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

Ácido ciclohexanosulfónico {4-fluoro-3-[5-(3-metanosulfonil-fenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-fenilo}-amida;

Ácido ciclopentanosulfónico {4-fluoro-3-[5-(3-metanosulfonil-fenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-fenilo}-amida;

Ácido ciclohexanosulfónico {4-fluoro-3-[5-(3-metanosulfonilamino-fenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-fenilo}-amida;

Ácido ciclopentanosulfónico {4-fluoro-3-[5-(3-metanosulfonilamino-fenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-fenilo}-amida;

Ácido ciclopentanosulfónico [4-fluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)-fenilo]-amida;

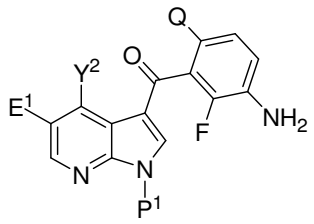
Ácido Piperidina-1-sulfónico [3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-4-fluoro-fenilo]-amida;

Ácido N,N-dimetilamino-sulfónico [3-(5-bromo-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-fenilo]-amida;

Ácido pirrolodina-1-sulfónico [3-(5-bromo-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-fenilo]-amida.

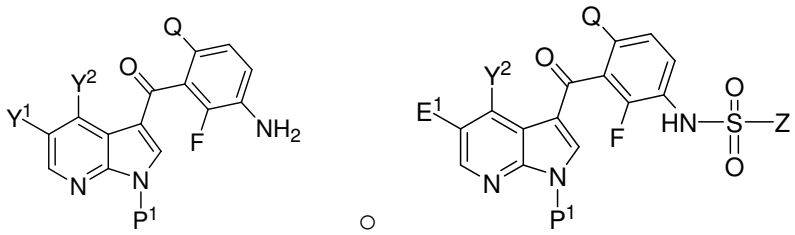
[0123] En otro aspecto, la presente invención proporciona un método de preparación de un compuesto de las fórmulas (I) a

(In). El método incluye poner en contacto un compuesto que tiene formula II:



II

Con un agente seleccionado de Y^1–G^1 (III) o a^1–$S(O)_2$–Z (IV) en condiciones suficientes para producir un compuesto que tiene las formulas (V) o (VI):



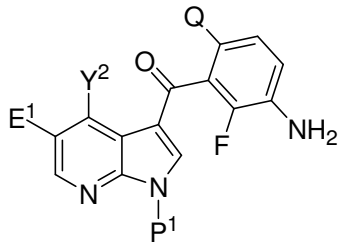
(V) o (VI)

Reacción de (i) un compuesto de fórmula (V) con un compuesto de fórmula (IV), o (ii) un compuesto de fórmula (VI) con un compuesto de fórmula (III) en condiciones suficientes para formar el compuesto de fórmula (I); y donde E^1 es halógeno, tosilato o mesilato; G^1 es $-B(OR^{25})_2$ o $-Sn(Bu)_3$, donde R^{25} es –OH, alquilo o dos sustituyentes $-OR^{25}$ junto con el átomo de boro a los cuales están unidos para formar un anillo de 5 o 6 miembros sustituido opcionalmente; A^1 es un grupo saliente, el cual puede desplazarse fácilmente mediante un grupo ariloamino; y P^1 es H o un grupo protector amino. En algunos casos, los sustituyentes del anillo de 5 o 6 miembros son grupos R^e de 1 a 4 miembros. En algunas realizaciones, la reacción de compuestos de fórmula (II), E^1 es

Cl, Br o I. En otra realización E^1 es tosilato, mesilato o triflato. En una realización, G^1 es $-B(OH)_2$. En otra realización, G^1 es 2-hidroxi-1,3,2-benzodioxaborole o 2-hidroxi-4,4,5,5-tetrametil-1,3,2-benzodioxaboro. En otra realización, G^1 es $-Sn(Bu)_3$. En una realización, A^1 es Cl o Br. En otra realización, A^1 es tosilato o mesilato. En una realización, P^1 es H. Los sustituyentes Y^1 y^2, Q y Z han sido definidos en cualquiera de las fórmulas (I) a (In) y cualquiera de las realizaciones reveladas en el presente documento.

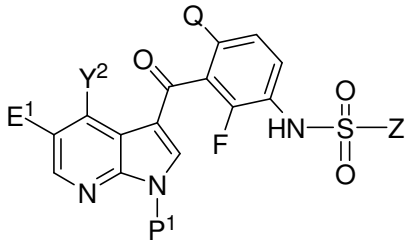
[0124] En algunas realizaciones, el método incluye poner en contacto un compuesto de fórmula (II) con un agente de fórmula (III): $Y^1-G^{1\ a}$ forman un compuesto de fórmula (V), seguido de la reacción de un compuesto de formula (V) con un agente de fórmula (IV): $A^1-S(O)_2-Z$ para producir un compuesto de fórmula (I). En otras realizaciones, el método incluye poner en contacto un compuesto de fórmula (II) con un agente de fórmula (IV): $A^1-S(O)_2-Z$ para producir un compuesto de fórmula (VI), seguido de la reacción de un compuesto de formula (VI) con un agente de fórmula (III): $Y^1-G^{1\ a}$ forman un compuesto de fórmula (I).

[0125] En otras realizaciones adicionales, la invención proporciona un método de preparación de un compuesto de fórmulas (I) a (In). El método incluye la reacción de un compuesto que tiene formula II:



II

con un compuesto de fórmula (IV): A^1–$S(O)_2$–Z en condiciones suficientes para producir un compuesto que tiene formula (VI):

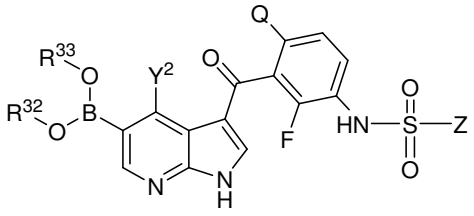


(VI)

poner en contacto un compuesto de fórmula (VI) con un compuesto de la formula: Y^1–E^2 y un compuesto de la formula: $(OR^{31})_2B$–$B(OR^{31})_2$ en presencia de un complejo de paladio en condiciones suficientes para producir el compuesto de fórmula (I), donde R^{31} es –OH, alquilo o dos $-OR^{31}$ sustituyentes junto con el átomo de boro a los cuales están unidos para producir un anillo de 5 o 6 miembros; y donde E^1 y E^2 son cada uno por separado halógeno, tosilato o mesilato; A^1 es un grupo saliente; y P^1 es H o un grupo protector amino. Ambos complejos Pd(0) y Pd(II) pueden ser usados. En algunas realizaciones, E^1 es Cl, Br, I, tosilato o mesilato. En algunas realizaciones, E^2 es Cl, Br, I, tosilato o mesilato. En ciertos casos, los complejos de paladio incluyen, no taxativamente, $Pd(PPh_3)_4$, bis(difenilofosfino)ferroceno]dicloropaladio y otros semejantes.

Los sustituyentes Y^1 y^2, Q y Z han sido definidos en in cualquiera de las fórmulas (I) a (In) y cualquiera de las realizaciones reveladas en el presente documento.

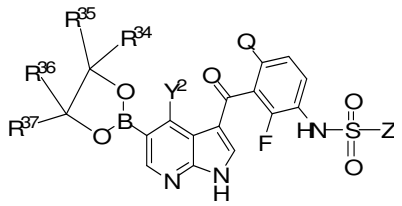
[0126] En otro aspecto, la invención proporciona un compuesto que tiene formula (VIII):



VIII

donde R^{32} y R^{33} son cada uno por separado H, alquilo sustituido opcionalmente, ariloalquilo sustituido opcionalmente o arilo Sustituido opcionalmente. En otras realizaciones, la porción de arilo o alquilo de R^{32} o R^{33} es sustituida opcionalmente con 1 a 4 sustituyentes R^e; o R^{32} y R^{33} junto con los átomos de oxígeno a los cuales están unidos forman un anillo de 5 o 6 miembros, donde el anillo de 5 o 6 miembros es sustituido opcionalmente con 1 a 4 grupos R^e o fusionados con un anillo aromático de 5 o 6 miembros. Los sustituyentes Y^2, Q y Z en la formula VIII han sido definidos en cualquiera de las fórmulas (I) a (In) y cualquiera de las realizaciones según se describen en este documento.

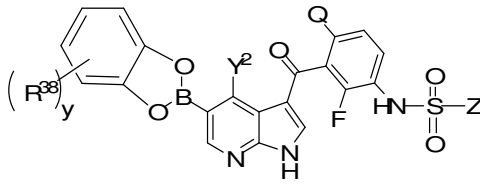
[0127] En algunas realizaciones, los compuestos de fórmula VIII tienen la subfórmula VIIIa:



VIIIa

R^{34}, R^{35}, R^{36} y R^{37} son cada uno por separado R^e o R^f. En ciertos casos, R^{34}, R^{35}, R^{36} y R^{37} son cada uno por separado C_{1-6} alquilo. En otros casos, R^{34}, R^{35}, R^{36} y R^{37} are CH_3. Los sustituyentes Y^2, Q y Z en la formula VIIIa han sido definidos en cualquiera de las fórmulas (I) a (In) y cualquiera de las realizaciones según se describen en este documento.

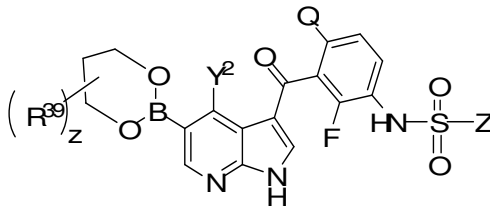
[0128] En algunas realizaciones, los compuestos de fórmula VIII tienen la subfórmula VIIIb:



VIIIb

El subíndice y es un número entero de 1 a 4. Cada R^{38} es por separado H, R^e o R^f. Los sustituyentes Y^2, Q y Z en la formula VII-Ib han sido definidos en in cualquiera de las fórmulas (I) a (In) y cualquiera de las realizaciones según se describen en este documento.

[0129] En algunas realizaciones, los compuestos de fórmula VIII tienen la subfórmula VIIIc:



VIIIc

El subíndice z es un número entero de 1 a 4. Cada R^{39} es por separado H, R^e o R^f. Los sustituyentes Y^2, Q y Z en la formula VIIIc han sido definidos en cualquiera de las fórmulas (I) a (In) y cualquiera de las realizaciones según se describen en este documento.

Técnicas sintéticas orgánicas

[0130] Existe una amplia gama de técnicas sintéticas orgánicas en la tecnología diseñadas para facilitar la preparación de moduladores potenciales. Muchos de estos métodos sintéticos orgánicos se describen detalladamente en fuentes de referencia convencionales usadas por las personas capacitadas en la tecnología. Un ejemplo de dicho material de referencia es de Marzo de 1994, Advanced Organic Chemistry; Reactions, Mechanisms and Structure, New York, McGraw Hill. Por ende, las técnicas útiles para sintetizar un modulador potencial de la función de quinasa están a la mano de las personas capacitadas en la tecnología de síntesis química orgánica.

Formas o derivados de compuesto alternativos

[0131] Los compuestos contemplados en el presente documento se describen con referencia a compuestos tanto de fórmula genérica como específicos. Adicionalmente, los compuestos de la in-

vención pueden existir en un número de diferentes formas o derivados, todos dentro del alcance de la presente invención. Las formas alternativas de derivados, incluyen, por ejemplo, (a) prodrogas y metabolitos activos (b) tautómeros, isómeros (incluyendo estereoisómeros y regioisómeros) y mezclas racémicas (c) sales aceptables farmacéuticamente y (d) formas sólidas incluyendo diferentes formas de cristal, sólidos polimórficos o amorfos, incluyendo hidratos y solvatos de los mismos y otras formas.

(a) *Prodrogas y metabolitos*

[0132] Adicionalmente a las presentes fórmulas y compuestos descritos en este documento, la invención también incluye prodrogas (generalmente prodrogas aceptables farmacéuticamente), derivados metabólicos activos (metabolitos activos) y sus sales aceptables farmacéuticamente.

[0133] Las prodrogas son compuestos o sales de los mismos aceptables farmacéuticamente que al ser metabolizadas en condiciones fisiológicas o convertidas mediante solvólisis producen el compuesto activo deseado. Las prodrogas incluyen, no taxativamente, ésteres, amidas, carbamatos, carbonatos, ureidos, solvatos o hidratos del compuesto activo. Normalmente, la prodroga es inactiva, o menos activa que el compuesto activo, pero puede proporcionar una o más propiedades ventajosas de manejo, administración y/o metabólicas. Por ejemplo, algunas prodrogas son ésteres del compuesto activo; durante la metabólisis, el grupo

éster es segmentado para producir la droga activa. Los ésteres incluyen, por ejemplo, ésteres de un grupo de ácido carboxílico, o derivados de S-acilo o O-acilo de grupos tiol, alcohol o fenol. En este contexto, un ejemplo frecuente es un éster de alquilo de un ácido carboxílico. Las prodrogas también pueden incluir variantes donde un grupo –NH del compuesto ha sido sometido a acilación, como por ejemplo la posición 1 del anillo 1H-pirrolo[2,3-b]piridina o el nitrógeno del grupo sulfonamida de compuestos según se describen en este documento, donde la segmentación del grupo acilo proporciona el grupo de –NH libre de la droga activa. Algunas prodrogas se activan enzimáticamente para producir el compuesto activo o un compuesto puede participar en una reacción química adicional para producir el compuesto activo. Las prodrogas pueden proceder de la forma de prodroga a la forma activa en un solo paso o pueden tener una o más formas intermedias las cuales pueden tener actividad o permanecer inactivas.

[0134] Según se describe en *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, CA, 2001), las prodrogas pueden dividirse conceptualmente en dos categorías no exclusivas, prodrogas bioprecursoras y prodrogas de soporte. En general, las prodrogas bioprecursoras son compuestos inactivos o de baja actividad en comparación con el compuesto de droga activo correspondiente, que contiene uno o más grupos protectores y son convertidos en una forma activa median-

te metabolismo o solvólisis. Tanto la forma de droga activa como cualesquiera productos metabólicas liberados deberían tener una toxicidad aceptablemente baja. Normalmente, la formación del compuesto de droga activo supone un proceso metabólico o una reacción, es decir uno de los tipos siguientes:

[0135] Reacciones oxidativas: Las reacciones oxidativas son ejemplificadas no taxativamente a través de reacciones como por ejemplo oxidación de alcohol, carbonilo y funcionalidades de ácido, hidroxilación de carbonos alifáticos, hidroxilación de átomos de carbono alicíclicos, oxidación de átomos aromáticos de carbono, oxidación de uniones dobles carbono-carbono, oxidación de grupos funcionales que contienen nitrógeno, oxidación de silicona, fósforo, arsénico y azufre, N-dealquilación oxidativa, O- y S-dealquilación oxidativa, desaminación oxidativa, así como otras reacciones oxidativas.

[0136] Reacciones reductoras: Las reacciones reductoras son ejemplificadas no taxativamente a través de reacciones como por ejemplo reducción de funcionalidades de carbonilo, reducción de funcionalidades de alcohol y uniones dobles carbono-carbono, reducción de grupos funcionales que contienen nitrógeno y otras reacciones de reducción.

[0137] Reacciones sin cambio en el estado de oxidación: Las reacciones sin cambio en el estado de oxidación son ejemplificadas no taxativamente a través de reacciones como por ejemplo hidrólisis de ésteres y éteres, segmentación hidrolítica de

uniones sencillas carbono-nitrógeno, segmentación hidrolítica de heterociclos no aromáticos, hidratación y deshidratación en uniones múltiples, nuevos enlaces atómicos que se obtienen de las reacciones de hidratación, deshalogenación hidrolítica, retirada de la molécula de haluro de hidrógeno y otras reacciones semejantes.

[0138] Las prodrogas de soporte son compuestos de droga que contienen una fracción de transporte, p. ej., que mejora la absorción y/o distribución localizada hacia un(os) sitio (s) de acción. En el caso de dichas prodrogas de soporte, lo deseable es que la unión entre la fracción de droga y la fracción de transporte sea una unión covalente, la prodroga sea inactiva o menos activa que el compuesto de droga, la prodroga y cualquier fracción de transporte de liberación sean aceptablemente no tóxicas. En el caso de prodrogas donde se busca que la fracción de transporte refuerce la absorción, normalmente la liberación de la fracción de transporte debería ser rápida. En otros casos, lo deseable sería utilizar una fracción que proporcione una liberación lenta, p. ej., ciertos polímeros u otras moléculas, como por ejemplo ciclodextrinas. (Ver, p. ej., Cheng et al., U.S. Patent Publ. No. 20040077595, App. No. 10/656,838, incorporadas al el presente documento mediante referencia.) Dichas prodrogas de soporte a menudo son ventajosas para drogas de administración oral. En algunos casos, la fracción de transporte proporciona una distribución de la droga enfocada en una meta, por ejemplo

la droga puede ser conjugada con un anticuerpo o fragmento de anticuerpo. Las prodrogas de soporte pueden por ejemplo, usarse para mejorar una o más de las propiedades siguientes: liofilicidad incrementada, duración incrementada de los efectos farmacológicos, especificidad por sitio incrementada, toxicidad y reacciones adversas disminuidas y/o mejoras en la formulación de la droga (p. ej., estabilidad, solubilidad en agua, supresión de una propiedad organoléptica o fisioquímica no deseada). Por ejemplo, se puede incrementar la lipofilicidad mediante esterificación de grupos hidroxilo con ácidos carboxílicos lipofílicos o de grupos de ácido carboxílicos con alcoholes, p. ej., alcoholes alifáticos. Wermuth, *supra*.

[0139] Los metabolitos, p. ej., metabolitos activos, se yuxtaponen con prodrogas según se describe anteriormente, p. ej., drogas bioprecursoras. Por ende, dichos metabolitos son compuestos activos farmacológicamente o compuestos que se metabolizan adicionalmente en compuestos activos farmacológicamente que son derivados obtenidos en procesos metabólicos en el cuerpo de un sujeto. De éstos, los metabolitos activos son dichos compuestos derivados activos farmacológicamente. En el caso de las prodrogas, el compuesto de prodroga es en general inactivo o de menor actividad que el producto metabólico. En el caso de metabolitos activos, el compuesto parental puede ser o bien un compuesto activo o puede ser una prodroga inactiva. Por ejemplo, en algunos compuestos, uno o más grupos alcoxi pueden metabolizarse en gru-

pos hidroxilo reteniendo su actividad farmacológica y/o grupos carboxilo pueden ser esterificados, p. ej., mediante glucuronidación. En algunos casos, puede haber más de un metabolito, donde un(os) metabolito(s) intermedio (s) se metaboliza para proporcionar un metabolito activo. Por ejemplo, en algunos casos, un compuesto derivado obtenido por glucuronidación metabólica puede ser inactivo o de baja actividad y puede metabolizarse adicionalmente para proporcionar un metabolito activo.

[0140] Los metabolitos de un compuesto pueden identificarse mediante técnicas de rutina conocidas en la tecnología y sus actividades se determinan a través de pruebas como por ejemplo las descritas en este documento. Véase, p. ej., Bertolini et al., 1997, *J. Med. Chem.*, 40:2011-2016; Shan et al., 1997, *J Pharm Sci* 86(7):756-757; Bagshawe, 1995, *Drug Dev. Res.*, 34:220-230; Wermuth, *supra*.

(b) *Tautómeros, Estereoisómeros y Regioisómeros*

[0141] Queda entendido que algunos compuestos pueden exhibir tautomerismo. En dichos casos, las fórmulas proporcionadas en el presente documento representan expresamente únicamente una de las posibles formas tautoméricas. En consecuencia, queda entendido que las fórmulas proporcionadas en el presente documento pretenden representar cualquier forma tautomérica de los compuestos representados y no se limitan meramente a la forma tautomérica especifica representada por las ilustraciones de las fórmulas.

[0142] De la misma manera, algunos de los compuestos de conformidad con la presente invención pueden existir como estereoisómeros, es decir, tienen la misma conectividad atómica de átomos unidos por covalencia pero difieren en la orientación espacial de los átomos. Por ejemplo, los compuestos pueden ser estereoisómeros ópticos, los cuales contienen uno o más centros quirales y, en consecuencia, pueden existir en dos o más formas estereoisoméricas (p.ej. enantiómeros o diastereómeros). Así, dichos compuestos pueden presentarse como estereoisómeros sencillos (es decir, esencialmente exentos de otros estereoisómeros), racematos y/o mezclas de enantiómeros y/o diastereómeros. Otro ejemplo: los estereoisómeros incluyen isómeros geométricos, como por ejemplo orientación *cis*- o *trans*- de sustituyentes en carbonos adyacentes de una unión doble. Todos estos estereoisómeros, racematos y mezclas de los mismos deben estar dentro del alcance de la presente invención. Salvo que se especifique lo contrario, todas dichas formas esteroisoméricas están incluidas dentro de las fórmulas proporcionadas en el presente documento.

[0143] En algunas realizaciones, un compuesto quiral de la presente invención está en una forma que contiene como mínimo 80% de un isómero sencillo (60% exceso enantiomérico (“e.e.”) o exceso diastereomérico (“d.e.”), o como mínimo 85% (70% e.e. o d.e.), 90% (80% e.e. o d.e.), 95% (90% e.e. o d.e.), 97,5% (95% e.e. o d.e.) o 99% (98% e.e. o d.e.). Según lo que prevalece generalmente entre las personas capacitadas en la tecnología, un

compuesto ópticamente puro que tiene un centro quiral es aquel que consiste esencialmente en uno de los dos enantiómeros posibles (es decir, es puro enantioméricamente) y un compuesto puro ópticamente que tiene más de un centro quiral es tanto diastereoméricamente puro como enantioméricamente puro. En algunas realizaciones, el compuesto está presente en forma ópticamente pura, dicha forma ópticamente pura es preparada y/o aislada mediante métodos conocidos en la tecnología (p.ej. mediante técnicas de recristalización, técnicas sintéticas quirales (incluyendo síntesis de materia prima ópticamente pura) y separación cromatográfica usando una columna quiral.

(c) *Sales aceptables farmacéuticamente*

[0144] Salvo que se especifique lo contrario, la especificación de un compuesto en el presente documento incluye sales de dicho compuesto aceptables farmacéuticamente. Por ende, los compuestos descritos en este documento y enumerados en cualquiera de las reivindicaciones pueden estar en forma de sales aceptables farmacéuticamente o pueden estar formulados como sales aceptables farmacéuticamente. Las formas de sal aceptables farmacéuticamente contempladas incluyen, no taxativamente, mono, bis, tris, tetraquis y así sucesivamente. Las sales aceptables farmacéuticamente son no tóxicas en las cantidades y concentraciones en las cuales se administran. La preparación de dichas sales puede facilitar el uso farmacológico mediante la alteración de características físicas de un compuesto sin impedirle

que ejerza su efecto fisiológico. Las alteraciones útiles de propiedades físicas incluyen la disminución del punto de fusión para facilitar la administración transmucosa y el incremento de la solubilidad para facilitar la administración en concentraciones más altas de la droga. Un compuesto de la invención puede poseer grupos funcionales suficientemente acídicos, suficientemente básicos o ambos, y por lo tanto pueden reaccionar con cualquier cantidad de bases inorgánicas u orgánicas y ácidos inorgánicos y orgánicos para producir una sal aceptable farmacéuticamente.

[0145] Las sales aceptables farmacéuticamente incluyen sales de adición de ácido como por ejemplo aquellas que contienen cloruro, bromuro, yoduro, hidrocloruro, acetato, feniloacetato, acrilato, ascorbato, aspartato, benzoato, 2-fenoxibenzoato, 2-acetoxibenzoato, dinitrobenzoato, hidroxibenzoato, metoxibenzoato, metilbenzoato, bicarbonato, butina-1,4 dioato, hexina-1,6-dioato, caproato, caprilato, clorobenzoato, cinnamato, citrato, decanoato, formato, fumarato, glicolato, gluconato, glucarato, glucuronato, glucosa-6-fosfato, glutamato, heptanoato, hexanoato, isetionato, isobutirato, gamma-hidroxibutirato, fenilobutirato, lactato, malato, maleato, hidroximaleato, metilmaleato, malonato, mandelato, nicotinato, nitrato, isónicotinato, octanoato, oleato, oxalato, pamoato, fosfato, monohidrógenofosfato, dihidrógenofosfato, ortofosfato, metafosfato, pirofosfato, 2-fosfoglicerato, 3-fosfoglicerato, ftalato, propionato, fenilo-

propionato, propiolato, piruvato, quinato, salicilato, 4-aminosalicilato, sebacato, estearato, suberato, succinato, sulfato, pirosulfato, bisulfato, sulfito, bisulfito, sulfamato, sulfonato, bencenosulfonato (es decir, besilato), etanosulfonato (es decir, esilato), etano-1,2-disulfonato, 2-hidroxietanosulfonato (es decir, isetionato), metanosulfonato (es decir, mesilato), naftaleno-1-sulfonato, naftaleno-2-sulfonato (es decir, napsilato), propanosulfonato, *p*-toluenosulfonato (es decir, tosilato), xilenesulfonatos, ciclohexilosulfamato, tartrato y trifluoroacetato. Estas sales de adición de ácido aceptables farmacéuticamente pueden prepararse usando el ácido correspondiente apropiado.

[0146] Cuando están presentes grupos funcionales acídicos, como por ejemplo ácido carboxílico o fenol, las sales aceptables farmacéuticamente también incluyen sales de adición de base como por ejemplo aquellas que contienen benzatina, cloroprocaina, colina, etanolamina, dietanolamina, trietanolamina, t-butilamina, diciclohexiloamina, etilenodiamina, N,N'-dibenciloetilenodiamina, meglumina, hidroxietilpirrolodina, piperidina, morfolina, piperacina, procaína, aluminio, calcio, cobre, hierro, litio, magnesio, manganeso, potasio, sodio, zinc, amonio y mono-, di-, o tri-alquiloaminas (p.ej. dietilamina), o sales derivadas de aminoácidos como por ejemplo L-histidina, L-glicina, L-lisina y L-arginina. Por ejemplo, véase *Remington's Pharmaceutical Sciences*, 19th ed., Mack Publishing Co., Easton,

PA, Vol. 2, p. 1457, 1995. Estas sales de adición de base aceptables farmacéuticamente pueden prepararse usando la base correspondiente apropiada.

[0147] Las sales aceptables farmacéuticamente pueden prepararse mediante técnicas convencionales. Por ejemplo, la forma de base libre de un compuesto pueden disolverse en un solvente adecuado, como por ejemplo una solución acuosa o de alcohol-acuosa que contiene el ácido apropiado y seguidamente aislada evaporando la solución. En otro ejemplo, se puede preparar una sal haciendo reaccionar la base libre y el ácido en un solvente orgánico. De ser el compuesto particular un ácido, la sal deseada aceptable farmacéuticamente puede prepararse a través de cualquier método adecuado, por ejemplo, tratamiento del ácido libre con una base apropiada inorgánica u orgánica.

(d) *Otras formas de compuesto*

[0148] En el caso de agentes sólidos, queda entendido entre las personas capacitadas en la tecnología que los compuestos y sales pueden existir en diferentes formas de cristal o polimórficas o pueden formularse como cocristales o pueden estar en forma amorfa, o pueden ser cualquier combinación de las mismas (p.ej. parcialmente cristalina, parcialmente amorfa, o mezclas de polimorfas) todas las cuales pretenden estar dentro del alcance de la presente invención y fórmulas especificadas. En tanto que las sales se forman mediante adición de ácido/base, es decir, a una base libre o un ácido libre del compuesto de in-

terés forma una reacción ácido/base con una correspondiente base de adición o ácido de adición, respectivamente, para obtener una interacción de carga iónica, los cocristales son una especia química nueva, es decir, formada entre compuestos neutros, siendo el resultado el compuesto y una especie molecular adicional en la misma estructura de cristales.

[0149] En algunos casos, los compuestos de la invención forman complejos con un ácido o una base, incluyendo sales de adición de base como por ejemplo amonio, dietilamina, etanolamina, etilenodiamina, dietanolamina, t-butilamina, piperacina, meglumina; sales de adición de ácido, como por ejemplo acetato, acetilosalicilato, besilato, camsilato, citrato, formato, fumarato, glutarato, hidroclorato, maleato, mesilato, nitrato, oxalato, fosfato, succinato, sulfato, tartrato, tiocianato y tosilato; y aminoácidos como por ejemplo alanina, arginina, asparagina, ácido aspártico, cisteína, glutamina, ácido glutámico, glicina, histidina, isoleucina, leucina, lisina, metionina, feniloalanina, prolina, serina, treonina, triptófano, tirosina o valina. En la combinación del compuesto de la invención con el ácido o base, se forma preferiblemente un complejo amorfo en lugar de un material cristalino como por ejemplo una sal o cocristal normal. En algunos casos, la forma amorfa del complejo es facilitada por el procesamiento adicional, como por ejemplo secado por aspersión, métodos mecanoquímicos como por ejemplo compactación por rodillos o irradiación de microondas del compuesto parental mez-

clado con el ácido o la base. Dichos métodos pueden incluir también la adición de sistemas de polímeros iónicos y/o no iónicos, incluyendo, aunque no taxativamente, hidroxipropil metil celulosa acetato succinato (HPMCAS) y copolímero de ácido metacrílico (p.ej. Eudragit® L100-55), que estabiliza adicionalmente la naturaleza amorfa del complejo. Dichos complejos amorfos proporcionan varias ventajas. Por ejemplo, la disminución de la temperatura de fusión en relación con la base libre facilita el procesamiento adicional, como por ejemplo, la extrusión en caliente, para mejorar todavía más las propiedades biofarmacéuticas del compuesto. También, el complejo amorfo es fácilmente quebradizo, lo cual proporciona una compresión mejorada para la introducción del sólido en una cápsula o tableta.

[0150] Adicionalmente, las fórmulas pretenden cubrir formas hidratadas o solvatadas así como sin hidratar o sin solvatar de las estructuras identificadas. Por ejemplo, los compuestos indicados incluyen tanto formas hidratadas como no hidratadas. Otros ejemplos de solvatos incluyen las estructuras combinado con un solvente adecuado, como por ejemplo isopropanol, etanol, metanol, dimetil sulfóxido, etil acetato, ácido acético o etanolamina.

IV. Formulaciones y administración

[0151] En otro aspecto, la presente invención proporciona composiciones farmacéuticas que comprenden/incluyen un soporte o excipiente aceptable farmacéuticamente y un compuesto de la in-

vención descritos en este documento o una sal o solvato del mismo aceptable farmacéuticamente. En una realización ejemplo, la presente invención proporciona una formulación farmacéutica que comprende/incluye un compuesto según se describe en este documento. En una realización, el compuesto tiene cualquiera de las fórmulas I y Ia a In.

[0152] Los métodos y compuestos están normalmente destinados a la terapia de seres humanos. Sin embargo, pueden usarse también para tratar indicaciones similares o idénticas en sujetos animales. Los compuestos descritos en este documento pueden administrarse a través de rutas diferentes, incluyendo la inyección (es decir, parenteral, incluyendo intravenosa, intraperitoneal, subcutánea e intramuscular), oral, transdérmica, transmucosal, rectal o inhalable. Dichas formas de dosis debería permitir que el compuesto alcance las células meta. Otros factores son bien conocidos dentro de la tecnología e incluyen consideraciones como por ejemplo toxicidad y formas de dosis que retardan el compuesto o composición en cuanto a sus efectos. Las técnicas y formulaciones pueden encontrarse en general en Remington: *The Science and Practice of Pharmacy*, 21st edition, Lippincott, Williams y Wilkins, Philadelphia, PA, 2005 (incorporado al presente documento mediante referencia).

[0153] En algunas realizaciones, las composiciones comprenden soportes o excipientes aceptables farmacéuticamente, como por ejemplo refuerzos, aglomerantes, desintegrantes, deslizantes,

lubricantes, agentes complejantes, solubilizadores y surfactantes, los cuales pueden elegirse de modo que faciliten la administración del compuesto a través de una ruta en particular. Los ejemplos de soportes incluyen carbonato de calcio, fosfato de calcio, varios azúcares, como por ejemplo lactosa, glucosa, o sacarosa, tipos de almidón, derivados de celulosa, gelatina, lípidos, liposomas, nanopartículas y otros semejantes. Los soportes también incluyen líquidos compatibles fisiológicamente como solventes o para suspensiones, incluyendo, por ejemplo, soluciones estériles de agua para inyección (WFI), solución salina, solución de dextrosa, solución de Hank, solución de Ringer, aceites vegetales, aceites minerales, aceites animales, glicoles polietilénicos, parafina liquida y otros semejantes. Los excipientes pueden incluir también, por ejemplo, dióxido de silicona coloidal, gel de sílice, talco, silicato de magnesio, silicato de calcio, aluminosilicato de sodio, trisilicato de magnesio, celulosa pulverizada, macrocristalina celulosa, carboximetil celulosa, carboximetilcelulosa de sodio reticulada, benzoato de sodio, carbonato de calcio, carbonato de magnesio, ácido esteárico, estearato de aluminio, estearato de calcio, estearato de magnesio, estearato de zinc, fumarato de estearilo de sodio, siloide, stearowet C, óxido de magnesio, almidón, glicolato de almidón de sodio, monoestearato de glicerilo, dibehenato de glicerilo, palmitostearato de glicerilo, aceite de vegetal hidrogenado, aceite de semilla de algodón hidrogenado, aceite mineral de

aceite de semilla de ricino, glicol polietilenito (p.ej. PEG 4000-8000), glicol polioxietilénico, poloxámeros, povidona, crospovidona, sodio de croscarmelosa, ácido algínico, caseína, copolímero de divinilbenceno de ácido metacrílico, docusato de sodio, ciclodextrinas (p.ej. 2-hidroxipropil-.delta.-ciclodextrin), polisorbatos (p.ej. polisorbato 80), cetrimida, TPGS (d-alfa-tocoferilo polietilen glicol 1000 succinato), sulfato de laurilo de magnesio, sulfato de laurilo de sodio, polietileno glicol éteres, éster de ácido digraso de glicoles de polietileno o un éster de ácido de sorbitano de polioxialquileno (p. ej., éster de sorbitano polioxietilénico Tween®), ésteres de ácido graso de sorbitano de polioxietileno, éster de ácido graso de sorbitano, p.ej. un éster de ácido graso de sorbitano de un ácido graso como por ejemplo ácido oleico, esteárico o ácido palmítico, mannitol, xilitol, sorbitol, maltosa, lactosa, lactosa monohidrato o lactosa secada por aspersión, sacarosa, fructosa, fosfato de calcio, fosfato de calcio dibásico, fosfato de calcio tribásico, sulfato de calcio, dextratos, dextrano, dextrina, dextrosa, acetato de celulosa, maltodextrina, simeticona, polidextrosem, chitosán, gelatina, HPMC (hidroxipropil metil celulosas), HPC (hidroxipropil celulosa), hidroxietil celulosa y otros semejantes.

[0154] Las formulaciones farmacéuticas pueden presentarse en formas de dosis unitaria que contienen una cantidad predeterminada de ingrediente activo por dosis unitaria. Dicha unidad pue-

de contener, por ejemplo, 0,5 mg a 1 g, preferiblemente 1 mg a 700 mg, más preferiblemente 5 mg a 100 mg de un compuesto de la invención (como una base libre, solvato (incluyendo hidrato) o sal, en cualquier forma), dependiendo de la condición que se trata, la ruta de administración y la edad, peso y condición del paciente. Las formulaciones de dosis unitarias preferidas son aquellas que contienen una dosis diaria, dosis semanal, dosis mensual, una subdosis o una fracción apropiada de la misma, de un ingrediente activo. Más aún, dichas formulaciones farmacéuticas pueden prepararse mediante cualquiera de los métodos bien conocidos dentro de la tecnología farmacéutica.

[0155] Las formulaciones farmacéuticas pueden adaptarse para su administración a través de cualquier ruta adecuada, por ejemplo la oral (incluyendo cápsulas, tabletas, cápsulas rellenas de líquido, tabletas de desintegración, tabletas de liberación inmediata, prolongada y controlada, bandas orales, soluciones, jarabes, bucal y sublingual), rectal, nasal, inhalación, tópico (incluyendo transdérmica), ruta vaginal o parenteral (incluyendo subcutánea, intramuscular, intravenosa o intradérmica). Dichas formulaciones pueden prepararse mediante cualquier método conocido dentro de la tecnología farmacéutica, por ejemplo llevando a una vinculación del ingrediente activo con el (los) soporte (s), excipiente(s) o diluyente. En general, el soporte, excipiente o diluyente usado en la formulación farmacéutica es "no tóxico," lo cual significa que el mismo/los mismos se consideran

seguros para el consumo en la cantidad distribuida en la composición farmacéutica e "inerte" lo cual significa que los mismos no reaccionan de manera estimable con la actividad terapéutica del ingrediente activo o producen un efecto no deseado.

[0156] En algunas realizaciones, se puede usar la administración oral. Las preparaciones farmacéuticas para uso oral pueden formularse en formas de dosis orales convencionales como por ejemplo unidades discretas, cápsulas, tabletas y preparaciones líquidas, como por ejemplo jarabes, elixires y gotas concentradas. Los compuestos descritos en este documento pueden combinarse con excipientes sólidos, opcionalmente moliendo una mezcla obtenida y procesando la mezcla de gránulos, después de agregar auxiliares adecuados, de así desearlo, para obtener, por ejemplo, tabletas, tabletas recubiertas, cápsulas duras, cápsulas suaves, soluciones (p.ej. soluciones acuosas, alcohólicas o aceitosas) y otros semejantes. Los excipientes adecuados son, en particular, refuerzos como por ejemplo azúcares, incluyendo lactosa, glucosa, sacarosa, manitol o sorbitol; preparaciones de celulosa por ejemplo, almidón de maíz, almidón de trigo, almidón de arroz, almidón de papa, gelatina, goma de tragacanto, metil celulosa, hidroxipropilmetil-celulosa, sodio carboximetilcelulosa (CMC) y/o polivinilopirrolidona (PVP: povidona); excipientes aceitosos, incluyendo aceites vegetales y animales, como por ejemplo aceite de girasol, aceite de oliva o aceite de hígado de bacalao. Las formulaciones de dosis oral puede también contener

agentes de desintegración, como por ejemplo la polivinilpirrolidona reticulada, agar, o ácido algínico, o una sal de los mismos, como por ejemplo alginato de sodio; un lubricante, como por ejemplo, estearato de talco o magnesio; un plastificante, como por ejemplo glicerol o sorbitol; un edulcorante, como por ejemplo sacarosa, fructosa, lactosa o aspartamo; un agente de saborización natural o artificial, como por ejemplo menta negra, aceite de té del Canadá o sabor a cereza; tintes o pigmentos, los cuales pueden usarse para identificación o caracterización de diferentes dosis o combinaciones, como por ejemplo dosis unitarias. También se proporcionan núcleos de grageas con recubrimientos adecuados. Con esta finalidad, se pueden usar soluciones de azúcar concentrada, las cuales pueden contener opcionalmente, por ejemplo, goma arábiga, talco, poli-vinilpirrolidona, gel carbopol, glicol polietilénico y/o dióxido de titanio, soluciones de laca y solventes orgánicos adecuados o mezclas de solventes. Los fluidos orales, como por ejemplo soluciones, jarabes y elíxires pueden prepararse en forma de unidad de dosis de modo que una cantidad dada contenga una cantidad predeterminada del compuesto.

[0157] Las preparaciones farmacéuticas que pueden usarse oralmente incluyen cápsulas duras hechas de gelatina (“gelcaps”), así como cápsulas suaves, selladas hechas de gelatina y un plastificante, como por ejemplo glicerol o sorbitol. Las cápsulas duras pueden contener los ingredientes activos mezcla-

dos con un relleno como por ejemplo lactosa, aglomerantes como por ejemplo almidones y/o lubricantes como por ejemplo talco o estearato de magnesio y, opcionalmente, estabilizantes. En cápsulas suaves, los compuestos activos pueden ser disueltos o suspendidos en líquidos adecuados, como por ejemplo aceites grasos, parafina líquida o glicoles polietilénicos líquidos.

[0158] En algunas realizaciones, se puede usar la inyección (administración parenteral), *p. ej.*, intramuscular, intravenosa, intraperitoneal y/o subcutánea. Los compuestos descritos en este documento para inyección pueden formularse en soluciones líquidas estériles, preferiblemente en soluciones reguladoras o soluciones compatibles fisiológicamente, como por ejemplo solución salina, Solución de Hank o solución Ringer. Las dispersiones también pueden prepararse en soluciones no acuosas, como por ejemplo glicerol, glicol propilénico, etanol, glicoles polietilénicos líquidos, triacetina y aceites vegetales. Las soluciones también pueden contener un preservativo, como por ejemplo metilparabeno, propilparabeno, clorobutanol, fenol, ácido sórbico, timerosal y otros semejantes. Adicionalmente, los compuestos pueden formularse en forma sólida, incluyendo, por ejemplo, formas liofilizadas y redisueltas o suspendidas antes del uso. Las formulaciones pueden presentarse en recipientes de dosis unitaria o dosis múltiples, por ejemplo ampollas selladas y viales y pueden almacenarse en una condición liofilizada que re-

quiere únicamente agregar el soporte líquido estéril, por ejemplo agua para inyección, inmediatamente antes del uso.

[0159] En algunas realizaciones, se puede usar la administración transmucosal, tópica o transdérmica. En dichas formulaciones de compuestos descritos en este documento, se usan penetrantes apropiados a la barrera a permear. Dichos penetrantes se conocen ampliamente dentro de la tecnología e incluyen, por ejemplo, para administración transmucosal, sales con bilis y derivados de ácido fusídico. Adicionalmente, pueden usarse detergentes para facilitar la permeación. La administración transmucosal, por ejemplo, puede ser a través de aerosoles nasales o supositorios (rectales o vaginales). Las composiciones de compuestos descritos en este documento para administración tópica pueden formularse como aceites, cremas, lociones, ungüentos y otros semejantes mediante selección de soportes apropiados conocidos en la tecnología. Los soportes adecuados incluyen aceites vegetales o minerales, petrolato blanco (parafina suave blanca), grasas o aceites de cadena ramificada, grasas animales y alcohol de peso molecular alto (superior a C_{12}). En algunas realizaciones, los soportes se seleccionan de modo que el ingrediente activo sea soluble. Pueden incluirse también emulsificantes, estabilizantes, humectantes y antioxidantes así como agentes que impartan color o fragancia, de así desearlo. Las cremas de aplicación tópica se formularán preferiblemente a partir de una mezcla de aceite mineral, cera de abejas autoemulsificante y agua en la

cual se agrega la mezcla del ingrediente activo, disuelto en una cantidad pequeña de solvente (p. ej., un aceite). Adicionalmente, la administración por medios transdérmicos puede comprender un parche o compresa transdérmica como por ejemplo una venda impregnada con un ingrediente activo y opcionalmente uno o más soportes o diluyentes conocidos dentro de la tecnología. Para administrarse en forma de un sistema de distribución transdérmico, la administración de dosis será continua en lugar de intermitente a través del régimen de dosis.

[0160] En algunas realizaciones, los compuestos se administran como productos inhalables. Los compuestos descritos en este documento pueden formularse como polvo seco o una solución, suspensión, o aerosol adecuado. Los polvos y soluciones pueden formularse con aditivos adecuados conocidos dentro de la tecnología. Por ejemplo, los polvos pueden incluir una base de polvo adecuada como por ejemplo lactosa o almidón y las soluciones pueden comprender glicol propilénico, agua estéril, etanol, cloruro de sodio y otros aditivos, como por ejemplo sales de tampón, álcali y ácido. Dichas soluciones o suspensiones pueden administrarse inhalando por medio de aerosol, bomba, atomizador o nebulizador y otros semejantes. Los compuestos descritos en este documento pueden usarse también combinado con otras terapias inhaladas, por ejemplo corticosteroides como por ejemplo proprionato de fluticasona, dipropionato de beclometasona, acetónido de triamcinolona, budesonida y furoato de mometasona;

beta agonistas como por ejemplo albuterol, salmeterol y formoterol; agentes anticolinárgicos como por ejemplo bromuro de ipratroprio o tiotropio; vasodilatadores como por ejemplo treprostinal e iloprost; enzimas como por ejemplo DNAasa; proteínas terapéuticas; anticuerpos de inmunoglobulina; un sencilla o doble, siRNA; antibióticos como por ejemplo tobramicina; antagonistas de receptor mucarinico; antagonistas de leucotrieno; antagonistas de citoquina; inhibidores de proteasa; cromolina de sodio; nedocril sodio; y cromoglicato de sodio.

[0161] Las cantidades de diversos compuestos a administrar puede determinarse mediante procedimientos convencionales que toman en cuenta factores como por ejemplo la actividad del compuesto (*in vitro*, p.ej. el compuesto IC_{50} contra el objetivo, o la actividad *in vivo* en modelos de eficacia animal), resultados farmacocinéticas en modelos animales (p.ej. vida media biológica biodisponibilidad), la edad, tamaño y peso del sujeto y el trastorno vinculado con el sujeto. La importancia de estos y otros factores son bien conocidos entre las personas capacitadas en la tecnología. En general, una dosis estará en la gama de aproximadamente 0,01 a 50 mg/kg, también aproximadamente 0,1 a 20 mg/kg del sujeto en tratamiento. Se pueden usar dosis múltiples.

[0162] Los compuestos descritos en este documento también pueden usarse combinado con otras terapias para tratar la misma enfermedad. Dicha combinación incluye la administración de los compuestos y una o más terapéuticas en momentos diferentes o la

coadministración del compuesto y una o más terapias adicionales. En algunas realizaciones, se puede modificar la dosis por uno o más de los compuestos de la invención u otras terapéuticas usadas en combinación, p. ej., reducción de la cantidad dosificada relacionada con un compuesto o terapia usada individualmente, a través de métodos bien conocidos para la persona capacitada en la tecnología.

[0163] Queda entendido que el uso combinado incluye el uso con otras terapias, drogas, procedimientos médicos, etc., donde la otra terapia o procedimiento puede administrarse en momentos diferentes (p.ej. en un plazo breve, como por ejemplo en el transcurso de horas (p.ej. 1, 2, 3, 4-24 horas), o en el transcurso de un tiempo más prolongado (p.ej. 1-2 días, 2-4 días, 4-7 días, 1-4 semanas) que un compuesto descrito en este documento, o en el mismo momento que un compuesto descritos en este documento. El uso combinado también incluye el uso con una terapia o procedimiento médico, es decir administrado una vez o de manera no frecuente, como por ejemplo con cirugía, junto con un compuesto descrito en este documento administrado en el transcurso de un tiempo corto o un tiempo mas prolongado antes o después de la otra terapia o procedimiento. En algunas realizaciones, la presente invención proporciona la distribución de un compuesto descrito en este documento y una o más terapéuticas con fármacos distribuidos mediante una ruta de administración diferentes o por la misma ruta de administración. El uso combinado para cual-

quier ruta de administración incluye la distribución de un compuesto descrito en este documento y una o más terapéuticas farmacológicas distribuidas por la misma ruta de administración juntas en cualquier formulación, incluyendo formulaciones donde los dos compuestos se vinculan químicamente de manera que mantienen su actividad terapéutica cuando se administran. En un aspecto, la otra terapia farmacológica puede coadministrarse con un compuesto descrito en este documento. El uso combinado mediante coadministración incluye administración de coformulaciones o formulaciones de compuestos unidos químicamente o administración de dos o más compuestos en formulaciones separadas una de otra por un tiempo corto (p.ej. en el transcurso de 1 hora, 2 horas, 3 horas, hasta 24 horas), administrado por rutas iguales o diferentes. La coadministración de formulaciones separadas incluye coadministración por distribución por medio de un dispositivo, por ejemplo el mismo dispositivo inhalable, la misma jeringa, etc., o administración de dispositivos separados unos de otros por un tiempo corto. Las coformulaciones de un compuesto descrito en este documento y una o más terapias farmacológicas adicionales distribuidas por la misma ruta incluyen la preparación de los materiales juntos de modo que puedan ser administrados con un solo dispositivo, incluyendo los compuestos separados combinados en una formulación o compuestos modificados de modo que estén unidos químicamente pero mantengan su actividad biológica. Dichos compuestos unidos químicamente pueden tener una

vinculación, es decir, pueden mantenerse considerablemente *in vivo*, o la vinculación puede romperse *in vivo*, separando los dos componentes activos.

V. Objetivos de quinasa e indicaciones de la invención

[0164] Las proteína quinasas juegan papeles clave en la propagación de señales bioquímicas en diversas rutas biológicas. Han sido descritas más de 500 quinasas y se conoce que existen quinasas específicas implicadas en una amplia gama de enfermedades o estados (es decir, indicaciones), incluyendo por ejemplo, no taxativamente, cáncer, enfermedad cardiovascular, enfermedad inflamatoria, enfermedad neurológica y otras enfermedades. Como tales, las quinasas representan puntos de control importantes para la intervención terapéutica de moléculas pequeñas. Las proteína quinasas objetivo específicas contempladas por la presente invención están descritas en la tecnología, incluyendo, no taxativamente, las proteína quinasas según se describen en el número de serie de solicitud de patente estadounidense 11/473,347 (ver también, publicación PCT WO2007002433), quedando dicha revelación incorporada al presente documento mediante referencia puesto que se relaciona con dichos objetivo de quinasa, así como lo siguiente:

[0165] **A-Raf:** Quinasa objetivo A-Raf (es decir, homólogo I de oncogén viral v-raf de sarcoma murino 3611) es una 67,6 kDa serina/treonina quinasa codificada por el cromosoma Xp11,4-p11,2 (símbolo: ARAF). La proteína madura comprende RBD (es decir, do-

minio de unión a Ras) y dominio de dedo de zinc de éster de forbol/tipo DAG y participa en la transducción de señales mitogénicas de la membrana celular hasta el núcleo. Los inhibidores de A-Raf pueden ser útiles en el tratamiento de enfermedades neurológicas como por ejemplo demencia por infarto múltiple, lesión de cabeza, lesión de la médula espina, Enfermedad de Alzheimer (AD), Enfermedad de Parkinson; enfermedades neoplásicas incluyendo, aunque no taxativamente, melanoma, glioma, sarcoma, carcinoma (p.ej. colorrectal, pulmón, mama, pancreático, tiroide, renal, ovárico), linfoma (p.ej. linfoma histiocítico), neurofibromatosis, síndrome mielodisplásico, leucemia, angiogénesis tumoral; dolor de origen neuropático o inflamatorio, incluyendo dolor agudo, dolor crónico, dolor relacionado con cáncer y migraña; y enfermedades vinculadas con regeneración o degeneración muscular, incluyendo, aunque no taxativamente, restenosis vascular, sarcopenia, distrofias musculares (incluyendo, aunque no taxativamente, distrofias musculares Duchenne, Becker, Emery-Dreifuss, Limb-Girdle, Facioscapulohumeral, Miotónica, Oculofaríngea, Distal y Congénito), enfermedades neuronales motoras (incluyendo, aunque no taxativamente, esclerosis lateral amiotrófica, atrofia muscular espinal progresiva infantil, atrofia muscular espinal intermedia, atrofia muscular espinal juvenil, atrofia muscular bulbar espinal y atrofia muscular espinal del adulto), miopatías inflamatorias (incluyendo, aunque no taxativamente, dermatomiositis, polimiositis e miositis con

cuerpos de inclusión), enfermedades de la unión neuromuscular (incluyendo, aunque no taxativamente, miastenia gravis, Síndrome de Lambert-Eaton y síndrome miasténico congénito), miopatías debido a anormalidades endocrinas (incluyendo, aunque no taxativamente, miopatía hipertiroidea e miopatía hipotiroidea) enfermedades del nervio periférico (incluyendo, aunque no taxativamente, Enfermedad de Charcot-Marie-Tooth, Enfermedad de Dejerine-Sottas y Ataxia de Friedreich), otras miopatías (incluyendo, aunque no taxativamente, miotonia congénita, paramiotonia congénita, enfermedad de los cuerpos centrales, miopatía nemalina, miopatía miotubular y parálisis periódica) y enfermedades metabólicas de los músculos (incluyendo, aunque no taxativamente, deficiencia de fosforilasa, deficiencia de maltasa ácida, deficiencia de fosfofructoquinasa, deficiencia de enzima desarborizadora, miopatía mitocondrial, deficiencia de carnitina, deficiencia de transferasa de palmatilo de carnitina, deficiencia de quinasa de fosfoglicerato, deficiencia de fosfoglicerato mutasa, deficiencia de lactato deshidrogenasa y deficiencia de mioadenilato desaminasa).

[0166] **B-Raf:** Quinasa objetivo B-Raf (es decir, homólogo B1 de oncogén viral v-raf de sarcoma murino) es una 84,4 kDa serina/treonina quinasa codificada por cromosoma 7q34 (símbolo: BRAF). La proteína madura comprende los dominios RBD (es decir, dominio de unión a Ras), C1 (es decir, región conservada 1 proteína quinasa C) y STK (es decir, serina/treonina quinasa).

[0167] La quinasa objetivo B-Raf participa en la transducción de señales mitogénicas de la membrana celular hasta el núcleo y puede jugar un papel en las respuestas postsinápticas de neuronas del hipocampo. Como tales, los genes de la familia RAF codifican quinasas que están reguladas por Ras y median respuestas celulares a las señales de crecimiento. De hecho, B-Raf quinasa es un componente clave de la ruta de señalización RAS->Raf-> MEK->ERK/MAP quinasa , la cual juega un papel fundamental en la regulación del crecimiento, división y proliferación celular y, cuando se activan constitutivamente, causan tumorigénesis. Entre diversas isoformas de Raf quinasa, el tipo B, o B-Raf, es el activador más fuerte de la señalización MAP quinasa aguas abajo.

[0168] El gen BRAF muta frecuentemente en una diversidad de tumores humanos, especialmente en el melanoma maligno y carcinoma de colon. La mutación más frecuente de la cual se tienen informes fue una transversión sin sentido de timina (T) a adenina (A) en el nucleótido 1796 (T1796A; cambio de áminoácidos en la proteína B-Raf es Val<600> a Glu<600>) observado en 80% de tumores malignos de melanoma. El análisis funcional revela que esta transversión es la única mutación detectada que causa la activación constitutiva de actividad de quinasa B-Raf, independiente de la activación de RAS, al convertir B-Raf en una proteína transformadora dominante. Con base en los precedentes, los tumores humanos desarrollan resistencia a los inhibidores de quinasa al mutar un aminoácido específico en el dominio catalítico como

“guardián”. (Balak, et. al., Clin Cancer Res. 2006, 12:6494-501). Se anticipa así la mutación de Thr-529 en BRAF a Ile como un mecanismo de resistencia ante los inhibidores BRAF y lo anterior puede imaginarse como una transición en el codón 529 de ACC a ATC.

[0169] Niihori et al., informa que en 43 individuos con síndrome cardio-facio-cutáneo (CFC), identificaron dos mutaciones KRAS heterocigóticas en tres individuos y ocho mutaciones BRAF en 16 individuos, sugiriendo que la desregulación de la ruta RAS-RAF-ERK es una base molecular común para los tres trastornos relacionados (Niihori et al., Nat Genet. 2006, 38(3):294-6).

[0170] Muchos tipos de cáncer vinculados con la desregulación de la ruta RAS-RAF-ERK, como por ejemplo el cáncer que tiene B-Raf V600, como por ejemplo mutaciones V600E o mutaciones NRAS, pueden tratarse con inhibidores de Raf quinasas, como por ejemplo los pan inhibidores de Raf quinasas según se describen en este documento. La capacidad de estos compuestos de inhibir múltiples objetivos de Raf quinasa, incluyendo c-Raf-1, B-Raf y B-Raf V600, como por ejemplo V600E, proporciona beneficios adicionales para inhibir la activación de mutaciones en esta ruta, con aquellos tipos de cáncer menos propensos a desarrollar resistencia a dichos inhibidores puesto que están seleccionando como meta varios puntos en la ruta. Los pan inhibidores de Raf quinasas según se describen en este documento pueden ser útiles

en tratar una diversidad de tipos de cáncer, incluyendo, aunque no taxativamente, melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, carcinoma (p.ej. gastrointestinal, hígado, tracto biliar, canal biliar (colangiocarcinoma), colorrectal, pulmón, cerebro, vejiga, vesícula biliar, mama, pancreático, tiroide, riñón, ovárico, adrenocortical, próstata), tumores estromales gastrointestinales, cáncer de tiroides medular, angiogenesis tumoral, leucemia mieloide aguda, leucemia mielomonocítica crónica, leucemia linfoblástica aguda de la infancia, leucemia de células plasmáticas y mieloma múltiple. Véase McDermott et al., PNAS, 2007, 104(50): 19936-19941; y Jaiswal et al., PLoS One, 2009, 4(5):e5717.

[0171] **c-Raf-1:** Quinasa objetivo c-Raf-1 (es decir, homólogo de oncogén viral v-raf de sarcoma murino) es una 73,0 kDa STK codificada por cromosoma 3p25 (símbolo: RAF1). La c-Raf-1 puede ser dirigida a la mitocondria por BCL2 (es decir, leucemia de células B oncogén 2) el cual es un regulador de muerte celular apoptótica. La c-Raf-1 activa mejora la resistencia a apoptosis mediada por BCL2 y C-Raf-1 fosforilatos BAD (es decir, proteína de unión a BCL2). C-Raf-1 está implicada en carcinomas, incluyendo carcinoma de células colorrectales, ováricas, pulmonares y renales. C-Raf-1 está también implicada como un mediador importante de angiogenesis tumoral (Hood, J.D. et al., 2002, Science **296**, 2404). Los inhibidores de c-Raf-1 también pueden ser útiles para el tratamiento de la leucemia mieloide aguda y los

síndromes mielodisplásicos (Crump, Curr Pharm Des 2002, 8(25):2243-8). Los activadores c-Raf-1 pueden ser útiles como tratamiento de tumores neuroendocrinos, como por ejemplo cáncer de tiroides medular, carcinoide, cáncer pulmonar de células pequeñas y focromocitoma (Kunnimalaiyaan et al., Anticancer Drugs 2006, 17(2):139-42).

[0172] Los inhibidores de Raf (A-Raf y/o B-Raf y/o c-Raf-1) pueden ser útiles en el tratamiento de enfermedades o estados mediados por A-Raf, mediados por B-Raf o mediados por C-Raf-1 seleccionados del grupo que consiste en enfermedades neurológicas, incluyendo, aunque no taxativamente, demencia por infarto múltiple, lesión de cabeza, lesión de la médula espina, Enfermedad de Alzheimer (AD), Enfermedad de Parkinson, crisis epilépticas y epilepsia; enfermedades neoplásicas incluyendo, aunque no taxativamente, melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, sarcoma, carcinoma (p.ej. gastrointestinal, hígado, tracto biliar, canal biliar (colangiocarcinoma), colorrectal, pulmón, cerebro, vejiga, vesícula biliar, mama, pancreático, tiroide, renal, ovárico, adrenocortical, próstata), linfoma (p.ej. linfoma histiocítico) neurofibromatosis, leucemia mieloide aguda, síndrome mielodisplásico, leucemia, leucemia mielomonocítica crónica, infancia, leucemia linfoblástica aguda, leucemia de células plasmáticas, mieloma múltiple, angiogenesis tumoral, tumores estromales gastrointestinales, tumores neuroendocrinos como por ejemplo cáncer de tiroides medular, carcinoi-

de, cáncer pulmonar de células pequeñas, Sarcoma de Kaposi y feocromocitoma; dolor de origen neuropático o inflamatorio, incluyendo, aunque no taxativamente, dolor agudo, dolor crónico, dolor relacionado con cáncer y migraña; enfermedades cardiovasculares incluyendo, aunque no taxativamente, insuficiencia cardiaca, ataque isquémico, hipertrofia cardiaca, trombosis (p.ej. síndromes de microangiopatía trombótica), ateroesclerosis y lesión por reperfusión; inflamación y/o proliferación incluyendo, aunque no taxativamente, soriasis, eczema, artritis y enfermedades y estados autoinmunes, osteoartritis, endometriosis, cicatrización, restenosis vascular, trastornos fibróticos, artritis reumatoidea, enfermedad inflamatoria del intestino (IBD); enfermedades provocadas por inmunodeficiencia, incluyendo, aunque no taxativamente, rechazo a transplante de órganos, enfermedad de injerto contra huésped y sarcoma de Kaposi vinculado con HIV; enfermedades renales, císticas o prostáticas, incluyendo, aunque no taxativamente, nefropatía diabética, enfermedad renal policística, nefrosclerosis, glomerulonefritis, hiperplasia prostática, enfermedad del hígado policística, esclerosis tuberosa, Enfermedad de Von Hippel Lindau, enfermedad del riñón cístico medular, nefronoftisis y fibrosis cística; trastornos metabólicos, incluyendo, aunque no taxativamente, obesidad; infección, incluyendo, aunque no taxativamente virus *Helicobacter pylori, Hepatitis* e *Influenza*, fiebre, HIV y septicemia; enfermedades pulmonares incluyendo, aunque no taxativamente, enferme-

dad pulmonar obstructiva crónica (COPD) y síndrome de insuficiencia respiratoria aguda (ARDS); enfermedades de desarrollo genético, incluyendo, aunque no taxativamente, Síndrome de Noonan, Síndrome de Costello, (síndrome de faciocutáneoesqueletal), síndrome de LEOPARD, síndrome cardio-faciocutáneo (CFC) y anomalías provocadas por el síndrome de crestas neurales que causan enfermedades cardiovasculares, esqueletales, intestinales, de la piel, el cabello y endocrinas; y enfermedades vinculadas con regeneración o degeneración muscular, incluyendo, aunque no taxativamente, sarcopenia, distrofias musculares (incluyendo, aunque no taxativamente, distrofias Duchenne, Becker, Emery-Dreifuss, Limb-Girdle, Facioscapulohumeral, Miotónica, Oculofaríngea, Distal y Congénito Muscular), enfermedades neuronales motoras (incluyendo, aunque no taxativamente, esclerosis lateral amiotrófica, atrofia muscular espinal progresiva infantil, atrofia muscular espinal intermedia, atrofia muscular espinal juvenil, atrofia muscular bulbar espinal y atrofia muscular espinal del adulto), miopatías inflamatorias (incluyendo, aunque no taxativamente, dermatomiositis, polimiositis y miositis con cuerpos de inclusión), enfermedades de la unión neuromuscular (incluyendo, aunque no taxativamente, miastenia gravis, Síndrome de Lambert-Eaton y síndrome miasténico congénito), miopatías debido a anormalidades endocrinas (incluyendo, aunque no taxativamente, miopatía hipertiroidea y miopatía hipotiroidea) enfermedades de los nervios periféricos (incluyendo, aunque no taxativamente, Enfer-

medad de Charcot-Marie-Tooth, Enfermedad de Dejerine-Sottas y Ataxia de Friedreich), otras miopatías (incluyendo, aunque no taxativamente, miotonia congénita, paramiotonia congénita, enfermedad de los cuerpos centrales, miopatía nemalina, miopatía miotubular y parálisis periódica) y enfermedades metabólicas de los músculos (incluyendo, aunque no taxativamente, deficiencia de fosforilasa, deficiencia de maltasa ácida, deficiencia de fosfofructoquinasa, deficiencia de enzima desarborizadora, miopatía mitocondrial, deficiencia de carnitina, deficiencia de transferasa de palmatilo de carnitina, deficiencia de quinasa de fosfoglicerato, deficiencia de fosfoglicerato mutasa, deficiencia de lactato deshidrogenasa y deficiencia de mioadenilato desaminasa).

[0173] **Erk2:** Quinasa objetivo Erk2 (es decir, quinasa 2 regulada por señal extracelular) es una 41,4 kDa serina/treonina-tirosina quinasa función dual codificada por cromosoma 22q11,2 (símbolo: MAPK1). Erk2 es un miembro de la familia de proteína quinasa activada por mitógeno (MAP) y se conoce de manera alternativa como proteína quinasa a activada por mitogeno (es decir, MAPK1). Las MAP quinasas actúan como un punto de integración para múltiples señales bioquímicas y participan en una amplia variedad de procesos celulares como por ejemplo proliferación, diferenciación, regulación de transcripción y desarrollo.

[0174] La activación de Erk2 requiere fosforilación por las quinasas aguas arriba. Después de la activación, Erk2 transloca

hasta el núcleo de las células estimuladas, donde fosforila objetivos nucleares, adicionalmente a otros objetivos incluyendo proteína 2 vinculada a microtúbulos, proteína básica de mielina y ELK1. MacKenzie et al. afirman que la familia 4 de fosfodiesterasa específica de cAMP-, subfamilia D, isoforma 3 (es decir, PDE4D3) tiene los puntos de acoplamiento de Erk2 FQF (es decir, Phe-Gln-Phe) y KIM (es decir, motivo de interacción de quinasa). Estos sitios abarcan el residuo objetivo Ser(579) para la fosforilación Erk2 de PDE4D3. La mutación de uno o ambos puntos de acoplamiento previenen la coninmunoprecipitación de Erk2 con PDE4D3, destruye la capacidad que tiene el factor de crecimiento epidérmico (EGF) de inhibir PDE4D3 a través de la acción Erk2 en células COS transfectadas y atenúan la capacidad que tiene Erk2 de fosforilar PDE4D3 in vitro. Se proponen los dos bloques de secuencia conservados NH(2)-terminal, denominados regiones conservadas aguas arriba 1 y 2 (es decir, UCR1 y UCR2), que caracterizan isoformas largas PDE4, para amplificar el efecto inhibitorio pequeño, inherente que la fosforilación de Erk2 ejerce sobre la unidad catalítica PDE4D. En contraste con lo anterior, la región UCR2 intacta aislada hallada en PDE4D1 dirige la fosforilación COOH-terminal Erk2 para causar la activación de esta isoforma corta. Del análisis de los truncados PDE4D3, se sugiere que UCR1 y UCR2 proporcionan un módulo de integración de señales reguladoras que sirve para orquestar las consecuencias funcionales de fosforilación Erk2. El gen PDE4D codifica, por ende, una

serie de isoenzimas que o bien son inhibidas activadas por la fosforilación Erk2 y mediante lo cual ofrece el potencial para la activación ERK2 o bien para incrementar o disminuir niveles cAMP en los compartimientos celulares (MacKenzie et al., J Biol Chem 2000, 275(22):16609-17).

[0175] De conformidad con OMIM, Pleschka et al. (Nature Cell Biol., 2001, 3: 301-305) propusieron que Erk2 regula un factor celular que participa en la función de proteína de exportación nuclear viral. Sugirieron que la aplicación local de inhibidores de MEK puede tener sólo efectos tóxicos sobre el huésped mientras inhiben la reproducción viral sin dar paso a variantes de virus resistentes a drogas (OMIM MIM Número: 176948: 10/27/2005). La Erk2 está involucrada en la señalización de citoquinas y es un objetivo para tratar la inflamación. Ramesh y Philipp afirman que las lipoproteínas son el tipo de molécula inflamatoria de Borrelia burgdorferi, la espiroqueta que causa la enfermedad de Lyme. Investigaron si la inhibición específica de p38 y Erk1/2 MAPK inhibirían la producción de TNF-alfa y IL-6 y, por ende, la apoptosis y proliferación de astrocitos, respectivamente. La producción de IL-6 estimulada por lipoproteínas no resultó afectada por los inhibidores de MAPK. En contraste, la inhibición tanto de p38 como de Erk1/2 disminuye significativamente la producción de TNF-alfa y deroga totalmente la producción de esta citoquina cuando ambas rutas MAPK eran inhibidas simultáneamente. La inhibición de MAPK puede ser considerada así

como una estrategia para controlar la inflamación y apoptosis en neuroborreliosis Lyme (Ramesh y Philipp, Neurosci Lett 2005, 384(1-2):112-6). El papel de Erk2 en la señalización de diferenciación, proliferación y sobrevivencia celular sugiere que la inhibición de Erk2 puede ser terapéutica en varios tipos de cáncer. Husain et al. estudió el efecto de NSAID en la actividad MAPK y la fosforilación en el cáncer gástrico. Concluyeron que NS-398 (un inhibidor selectivo de COX-2) e indometacina (NSAID no selectivo) inhiben significativamente la proliferación y crecimiento de la línea de células cancerígenos gástricas humanas MKN28. Este efecto es mediado por la inhibición de la ruta de señalización de MAPK (ERK2) quinasa inducida por NSAID, esencial para la proliferación celular (Husain et al., Life Sci 2001, 69(25-6):3045-54). Los inhibidores de Erk2 pueden ser útiles en el tratamiento del cáncer, incluyendo cáncer gástrico y en el tratamiento de la inflamación, incluyendo el control de la inflamación y la apoptosis en la neuroborreliosis Lyme.

Pruebas de la actividad de quinasa

[0176] Se puede utilizar una cantidad de diferentes pruebas para probar la actividad de quinasa en cuanto a moduladores activos y/o determinación de la especificidad de un modulador para una quinasa o grupo de quinasas en particular. Adicionalmente a la prueba mencionada en los ejemplos más adelante, la persona capacitada en la tecnología conoce otras pruebas que se pueden realizar y estará en capacidad de modificar una prueba para una

aplicación en particular. Por ejemplo, se pueden usar numerosos trabajos concernientes a quinasas que incluyen descripciones de pruebas de este tipo.

[0177] En ciertas realizaciones, los compuestos según se revelan en el presente documento son activos en una prueba que mide la actividad de quinasa en una proteína B-Raf. En algunas realizaciones, un compuesto según se describe en este documento tiene un IC_{50} inferior a 1,000 nM, inferior a 500 nM, inferior a 100 nM, inferior a 50 nM, inferior a 20 nM, inferior a 10 nM, inferior a 5 nM o inferior a 1 nM según se determina en una prueba de actividad de quinasa en B-Raf generalmente aceptada. En algunas realizaciones, un compuesto según se describe en este documento tiene un IC_{50} inferior a 1,000 nM, inferior a 500 nM, inferior a 100 nM, inferior a 50 nM, inferior a 20 nM, inferior a 10 nM, inferior a 5 nM, o inferior a 1 nM según se determina en una prueba de actividad de quinasa en B-Raf mutante generalmente aceptada (como por ejemplo V600A, V600M, V600R, V600E, V600K o V600G). En algunas realizaciones la prueba para medir la actividad de quinasa -Raf y/o B-Raf quinasa mutante (como por ejemplo V600A, V600M, V600R, V600E, V600K o V600G) incluye una prueba (p. ej., pruebas bioquímicas o de bases celulares) como por ejemplo la descrita en el Ejemplo 9 o una prueba bien conocida en la tecnología semejante a las descritas en el Ejemplo 9.

[0178] En algunas realizaciones, los compuestos según se describen en este documento tienen muy poca o ninguna actividad en una prueba que mide la activación de la ruta ERK (es decir, en la estimulación de la fosforilación de ERK 1/2). En algunas realizaciones, los compuestos según se describen en este documento tienen un EC_{50} en una prueba de activación de ERK que es mayor que 1 μM; o superior a 2 μM; o superior a 3 μM; o superior a 4 μM; o superior a 5 μM; o superior a 8 μM; o superior a 10 μM. En ciertas realizaciones, la prueba para medir la activación de la ruta ERK incluye una prueba (p. ej., pruebas bioquímicas o bases celulares) como por ejemplo las descritas en el Ejemplo 9 o una o más pruebas bien conocidas en la tecnología para medir actividad ERK semejantes a las descritas en el Ejemplo 9.

[0179] En algunas realizaciones, los compuestos según se describen en este documento son activos en una prueba que mide la actividad de quinasa en una proteína B-Raf y/o una prueba para medir la actividad de quinasa en la proteína B-Raf mutante (como por ejemplo V600A, V600M, V600R, V600E, V600K o V600G) y tienen muy poca o ninguna actividad en una prueba que mide la activación de la ruta ERK. En algunas realizaciones un compuesto según se describe en este documento tiene un IC_{50} inferior a 1,000 nM, inferior a 500 nM, inferior a 100 nM, inferior a 50 nM, inferior a 20 nM, inferior a 10 nM, inferior a 5 nM, o inferior a 1 nM según se determina en una prueba de actividad de quinasa en B-Raf generalmente aceptada (incluyendo una prueba de actividad de

quinasa en B-Raf mutante) y un EC_{50} en una prueba de activación de ERK es decir superior a 1 µM; o superior a 2 µM; o superior a 3 µM; o superior a 4 µM; o superior a 5 µM; o superior a 8 µM; o superior a 10 µM. En algunas realizaciones, un compuesto según se describe en este documento tiene un IC_{50} inferior a 100 nM en una prueba de actividad B-Raf mutante V600A, V600M, V600R, V600E, V600K o V600G y un EC_{50} superior a 10 en una prueba de activación de ERK.

VI. Métodos para tratar estados mediados por quinasas

[0180] En otro aspecto, la presente invención proporciona un método para tratar a un sujeto que padece de una enfermedad o estado mediado por proteína quinasas o presenta un riesgo de padecerlo. El método incluye administrar al sujeto una cantidad eficaz de un compuesto de cualquiera de las fórmulas I y Ia a In, o un compuesto según se describe en este documento, o una composición que comprende cualquiera de las fórmulas I y Ia a In y cualquiera de los compuestos descritos en este documento o una sal o solvato o hidrato del mismo aceptable farmacéuticamente. En ciertas realizaciones, el método supone administrar al sujeto una cantidad eficaz de cualquiera de uno o más compuesto (s) según se describen en este documento combinado con una o más terapias para la enfermedad o estado.

[0181] En algunas realizaciones, las enfermedades o estados tratables con los compuestos de la presente invención incluyen, no taxativamente, demencia por infarto múltiple, lesión de cabe-

za, lesión de la médula espina, Enfermedad de Alzheimer (AD), Enfermedad de Parkinson, crisis epilépticas y epilepsia; enfermedades neoplásicas incluyendo, aunque no taxativamente, melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, sarcoma, carcinoma (p.ej. gastrointestinal, hígado, tracto biliar, canal biliar (colangiocarcinoma), colorrectal, pulmón, vesícula biliar, mama, pancreático, tiroide, renal, ovárico, adrenocortical, próstata), linfoma (p.ej. linfoma histiocítico) neurofibromatosis, tumores estromales gastrointestinales, leucemia mieloide aguda, síndrome mielodisplásico, leucemia, angiogenesis tumoral, tumores neuroendocrinos como por ejemplo cáncer de tiroides medular, carcinoide, cáncer pulmonar de células pequeñas, Sarcoma de Kaposi y feocromocitoma; dolor de origen neuropático o inflamatorio, incluyendo, aunque no taxativamente, dolor agudo, dolor crónico, dolor relacionado con cáncer y migraña; enfermedades cardiovasculares incluyendo, aunque no taxativamente, insuficiencia cardiaca, ataque isquémico, hipertrofia cardiaca, trombosis (p.ej. síndromes de microangiopatía trombótica), ateroesclerosis y lesión por reperfusión; inflamación y/o proliferación incluyendo, aunque no taxativamente, soriasis, eczema, artritis y enfermedades y estados autoinmunes, osteoartritis, endometriosis, cicatrización, restenosis vascular, trastornos fibróticos, artritis reumatoidea, enfermedad inflamatoria del intestino (IBD); enfermedades provocadas por inmunodeficiencia, incluyendo, aunque no taxativamente, rechazo a transplante

de órganos, enfermedad de injerto contra huésped y Sarcoma de Kaposi vinculado con HIV; enfermedades renales, císticas o prostáticas, incluyendo, aunque no taxativamente, nefropatía diabética, enfermedad renal policística, nefrosclerosis, glomerulonefritis, hiperplasia prostática, enfermedad del hígado policística, esclerosis tuberosa, Enfermedad de Von Hippel Lindau, enfermedad del riñón cístico medular, nefronoftisis y fibrosis cística; trastornos metabólicos, incluyendo, aunque no taxativamente, obesidad; infección, incluyendo, aunque no taxativamente los virus *Helicobacter pylori, Hepatitis* e *Influenza*, fiebre, HIV y septicemia; enfermedades pulmonares incluyendo, aunque no taxativamente, enfermedad pulmonar obstructiva crónica (COPD) y síndrome de insuficiencia respiratoria aguda (ARDS); enfermedades de desarrollo genético, incluyendo, aunque no taxativamente, Síndrome de Noonan, Síndrome de Costello, (síndrome de facio-cutáneoesqueletal), síndrome de LEOPARD, síndrome cardio-faciocutáneo (CFC) y anomalías provocadas por el síndrome de crestas neurales que causa enfermedades cardiovasculares, esqueletales, intestinales, de la piel, el cabello y endocrinas; y enfermedades vinculado con regeneración o degeneración muscular, incluyendo, aunque no taxativamente, sarcopenia, distrofias musculares (incluyendo, aunque no taxativamente, Duchenne, Becker, Emery-Dreifuss, Limb-Girdle, Facioscapulohumeral, Miotonic, Oculofaríngeo, distrofias musculares distales y congénitas), enfermedades neuronales motoras (incluyendo, aunque no taxativamente,

esclerosis lateral amiotrófica, atrofia muscular espinal progresiva infantil, atrofia muscular espinal intermedia, atrofia muscular espinal juvenil, atrofia muscular bulbar espinal y atrofia muscular espinal del adulto), miopatías inflamatorias (incluyendo, aunque no taxativamente, dermatomiositis, polimiositis y miositis con cuerpos de inclusión), enfermedades de la unión neuromuscular (incluyendo, aunque no taxativamente, miastenia gravis, Síndrome de Lambert-Eaton y Síndrome miasténico congénito), miopatías debido a anormalidades endocrinas (incluyendo, aunque no taxativamente, miopatía hipertiroidea y miopatía hipotiroidea) enfermedades de los nervios periféricos (incluyendo, aunque no taxativamente, Enfermedad de Charcot-Marie-Tooth, Enfermedad de Dejerine-Sottas y Ataxia de Friedreich), otras miopatías (incluyendo, aunque no taxativamente, miotonia congénita, paramiotonia congénita, enfermedad de los cuerpos centrales, miopatía nemalina, miopatía miotubular y parálisis periódica) y enfermedades metabólicas de los músculos (incluyendo, aunque no taxativamente, deficiencia de fosforilasa, deficiencia de maltasa ácida, deficiencia de fosfofructoquinasa, deficiencia de enzima desarborizadora, miopatía mitocondrial, deficiencia de carnitina, deficiencia de transferasa de palmatilo de carnitina, deficiencia de quinasa de fosfoglicerato, deficiencia de fosfoglicerato mutasa, deficiencia de lactato deshidrogenasa y deficiencia de mioadenilato desaminasa). En una realización, la enfermedad o estado se selecciona del grupo que consiste en mela-

noma, glioma, glioblastoma multiforme, astrocitoma pilocítico, sarcoma, cáncer del hígado, cáncer del canal biliar, colangiocarcinoma, cáncer colorrectal, cáncer del pulmón, cáncer de la vesícula biliar, cáncer de mama, cáncer pancreático, cáncer de tiroides cáncer renal, cáncer ovárico, cáncer adrenocortical, cáncer de la próstata, linfoma histiocítico , neurofibromatosis, tumores estromales gastrointestinales, leucemia mieloide aguda, síndrome mielodisplásico, leucemia, angiogenesis tumoral, cáncer de tiroides medular, carcinoide, cáncer pulmonar de células pequeñas, Sarcoma de Kaposi, feocromocitoma, dolor agudo, dolor crónico y enfermedad renal policística. En una realización preferida, la enfermedad o estado se selecciona del grupo que consiste en melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, cáncer colorrectal, cáncer de tiroides, cáncer del pulmón, cáncer ovárico, cáncer de la próstata, cáncer del hígado, cáncer de la vesícula biliar, tumores estromales gastrointestinales, cáncer del canal biliar, colangiocarcinoma, dolor agudo, dolor crónico y enfermedad renal policística.

[0182] En otras realizaciones, las enfermedades o estados tratables con los compuestos de la presente invención incluyen, no taxativamente, ataque isquémico, isquemia cerebrovascular, demencia por infarto múltiple, lesión de cabeza, lesión de la médula espina, Enfermedad de Alzheimer, Enfermedad de Parkinson, esclerosis lateral amiotrófica, demencia, corea senil, Enfermedad de Huntington, enfermedad neoplásica, complicaciones con en-

fermedades neoplásicas, hipoxia inducida por quimioterapia, tumores estromales gastrointestinales, tumores de la próstata, tumores de mastocitos, tumores de los mastocitos en perros, leucemia mieloide aguda, leucemia linfótica agua, leucemia mieloide crónica, leucemia linfocítica crónica, mieloma múltiple, melanoma, mastocitosis, glioma, glioblastoma, astrocitoma, neuroblastoma, sarcomas, sarcomas de origen neuroectodérmico, leiomiosarcoma, carcinoma del pulmón, carcinoma de mama, carcinoma pancreático, carcinoma de colon, carcinoma hepatocelular, carcinoma renal, carcinoma del tracto genital femenino, carcinoma de células escamosas, carcinoma in situ, linfoma, linfoma histiocítico , linfoma no Hodgkin, síndromes MEN2, neurofibromatosis, meoplasia de la célula de Schwann, síndrome mielodisplásico, leucemia, angiogenesis tumoral, cáncer de tiroides, cáncer del hígado, cáncer de los huesos, cáncer de la piel, cáncer del cerebro, cáncer del sistema nervioso central, cáncer pancreático, cáncer del pulmón, cáncer pulmonar de células pequeñas, cáncer pulmonar de células no pequeñas, cáncer de mama, cáncer de colon, cáncer de vejiga, cáncer de la próstata, cáncer del tracto gastrointestinal, cáncer del endometrio, cáncer de las trompas de Falopio, cáncer testicular, cáncer ovárico, dolor de origen neuropático, dolor de origen inflamatorio, dolor agudo, dolor crónico, migraña, enfermedad cardiovascular, insuficiencia cardiaca, hipertrofia cardiaca, trombosis , síndromes de microangiopatía trombótica, ateroesclerosis, lesión por reperfusión, isquemia, isquemia

cerebrovascular, isquemia del hígado, inflamación, enfermedad renal policística, degeneración macular relacionada con la edad, artritis reumatoidea, rinitis alérgica, enfermedad inflamatoria del intestino, colitis ulcerosa, Enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren, granulomatosis de Wegener, soriasis, escleroderma, tiroiditis crónica, Enfermedad de Graves, miastenia gravis, esclerosis múltiple, osteoartritis, endometriosis, cicatrización dérmica, cicatrización de tejidos, restenosis vascular, trastornos fibróticos, hipereosinofilia, Inflamación de CNS, pancreatitis, nefritis, dermatitis atópica, hepatitis, enfermedades provocadas por inmunodeficiencia, inmunodeficiencia combinada grave, rechazo a transplante de órganos, enfermedad de injerto contra huésped, enfermedad renal, enfermedad prostática, nefropatía diabética, nefrosclerosis, glomerulonefritis, nefritis intersticial, nefritis lúpica, hiperplasia prostática, deficiencia renal crónica, necrosis tubular, complicación renal vinculada a diabetes, hipertrofia renal vinculada, diabetes tipo I, diabetes tipo 2, síndrome metabólico, obesidad, esteatosis hepática, resistencia a la insulina, hiperglicemia, lipolisis obesidad, infección, infección por *Helicobacter pylori*, infección por *Influenza virus,* fiebre, septicemia, enfermedades pulmonares, enfermedad pulmonar obstructiva crónica, síndrome de insuficiencia respiratoria aguda, asma, alergia, bronquitis, enfisema, fibrosis pulmonar, enfermedades de desarrollo genético, Síndrome de Noonan, Síndrome de Crouzon, acro-

cefalosindactilia tipo I, Síndrome de Pfeiffer, Síndrome de Jackson-Weiss, Síndrome de Costello, síndrome faciocutaneoesqueletal, síndrome de Leopard, síndrome cardio-faciocutáneo, anomalías provocadas por el síndrome de crestas neurales que causan enfermedades cardiovasculares, esqueletales, intestinales, de la piel, del cabello o endocrinas, trastornos de la estructura ósea o mineralización, osteoporosis, riesgo aumentado de fracturas, hipercalcemia, metástasis ósea, Enfermedad de Grave, Enfermedad de Hirschsprung, linfoedema, defecto selectivo en las células T, agammaglobulinemia congénita, retinopatía diabética, alopecia, disfunción eréctil y esclerosis tuberosa.

[0183] En algunas realizaciones, la enfermedad es un cáncer seleccionado del grupo que consiste en melanoma, glioma, glioblastoma, astrocitoma pilocítico, cáncer del hígado, cáncer del canal biliar, colangiocarcinoma, cáncer colorrectal, cáncer del pulmón, cáncer de vejiga, cáncer de la vesícula biliar, cáncer de mama, cáncer pancreático, cáncer de tiroides, cáncer del riñón, cáncer ovárico, cáncer adrenocortical, cáncer de la próstata, tumores estromales gastrointestinales, cáncer de tiroides medular, angiogenesis tumoral, leucemia mieloide aguda, leucemia mielomonocítica crónica, leucemia linfoblástica aguda de la infancia, leucemia de células plasmáticas y mieloma múltiple. En ciertos casos, la enfermedad es una enfermedad mediada por mutante B-Raf V600, como por ejemplo V600A, V600E, V600G, V600K, V600M o V600R. En una realización, la enfermedad es una

enfermedad mediada por mutante V600E. En una realización, la enfermedad es un cáncer, preferiblemente seleccionado del grupo que consiste en melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, cáncer colorrectal, cáncer de tiroides, cáncer del pulmón, cáncer ovárico, cáncer de la próstata, cáncer del hígado, cáncer de la vesícula biliar, tumores estromales gastrointestinales, cáncer del canal biliar y colangiocarcinoma. En una realización, el cáncer es melanoma, cáncer colorrectal, cáncer de tiroides o cáncer del pulmón.

[0184] En algunas realizaciones, la invención proporciona métodos para tratar cualquier enfermedad o estado mediado por B-Raf proteína quinasa, incluyendo cualquier enfermedad o estado mediado por mutante B-Raf en un animal que lo necesite, donde el método supone administrar al sujeto una cantidad eficaz de cualquiera de uno o más compuesto (s) según se describen en este documento. En ciertas realizaciones, el método supone administrar al sujeto animal que lo necesite una cantidad eficaz de cualquiera de uno o más compuesto (s) según se describen en este documento combinado con una o más terapias adicionales para la enfermedad o estado.

[0185] En algunas realizaciones, la invención proporciona métodos para tratar cualquier enfermedad o estado mediado por proteína quinasa mutante B-Raf V600, como por ejemplo V600A, V600E, V600G, V600K , V600M o V600R en un sujeto animal que lo necesite, donde el método supone administrar al sujeto una can-

tidad eficaz de cualquiera uno o más compuesto (s) según se describen en este documento. En ciertas realizaciones, el método supone administrar al sujeto una cantidad eficaz de cualquiera uno o más compuesto (s) según se describen en este documento combinado con una o más terapias adicionales para la enfermedad o estado.

[0186] En algunas realizaciones, un compuesto según se describe en este documento es un inhibidor de Raf quinasa y tiene un IC_{50} inferior a 500 nM, inferior a 100 nM, inferior a 50 nM, inferior a 20 nM, inferior a 10 nM, inferior a 5 nM, o inferior a 1 nM según se determina en una prueba generalmente aceptada De la actividad de quinasa de Raf. En algunas realizaciones, un compuesto según se describe en este documento tendrá un IC_{50} inferior a 500 nM, inferior a 100 nM, inferior a 50 nM, inferior a 20 nM, inferior a 10 nM, inferior a 5 nM, o inferior a 1 nM con respecto a B-Raf, c-Raf-1 o B-Raf V600E mutante. En algunas realizaciones, un compuesto según se describe en este documento inhibirá de manera selectiva uno o más Raf quinasas relativas a una o más otras quinasas Raf.

[0187] En algunas realizaciones, la invención proporciona un método para inhibir una proteína quinasa mutante B-Raf V600, como por ejemplo V600A, V600E, V600G, V600K , V600M o V600R. El método incluye poner en contacto un compuesto de cualquiera de las fórmulas I y Ia a In, o un compuesto según se describe en este documento, o una composición que comprende cualquiera de

las fórmulas I y Ia a In y cualquiera de los compuestos descritos en este documento o una sal o solvato de la misma aceptable farmacéuticamente con una célula o una proteína quinasa mutante B-Raf V600 o bien in vitro o in vivo.

[0188] En ciertas realizaciones, la invención proporciona el uso de un compuesto de cualquiera de las fórmulas I y Ia a In, o un compuesto según se describe en este documento, o una composición que comprende cualquiera de las fórmulas I y Ia a In y cualquiera de los compuestos descritos en este documento o una sal aceptable farmacéuticamente o un solvato de la misma en la preparación de un medicamento para el tratamiento de una enfermedad o estado según se describen en este documento. En otras realizaciones, la invención proporciona un compuesto de cualquiera de las fórmulas I y Ia a In, o un compuesto según se describe en este documento, o una composición que comprende cualquiera de las fórmulas I y Ia a In y cualquiera de los compuestos descritos en este documento o una sal aceptable farmacéuticamente o un solvato de la misma a usar en el tratamiento de una enfermedad o estado según se describen en este documento.

[0189] En algunas realizaciones, la invención proporciona un método para suprimir la apoptosis inducida por UV. El método incluye poner en contacto una célula con un compuesto de cualquiera de las fórmulas I y Ia a In o un compuesto según se describe en este documento o una composición que comprende cualquiera de las fórmulas I y Ia a In y cualquiera de los compuestos descri-

tos en este documento o una sal aceptable farmacéuticamente o un solvato de la misma antes de someter la célula a la exposición o radiación UV.

Multiterapia

[0190] Los moduladores de proteína quinasa pueden ser combinados de manera beneficiosa con otros compuestos activos farmacológicamente o con dos o más compuestos activos farmacológicamente, particularmente en el tratamiento de cáncer. En una realización, la composición incluye cualesquiera uno o más compuesto (s) según se describen en este documento junto con uno o más compuestos eficaces terapéuticamente para la misma indicación de enfermedad, donde los compuestos tienen un efecto sinérgico en la indicación de enfermedad. En una realización, la composición incluye cualesquiera uno o más compuesto (s) según se describen en este documento eficaces en el tratamiento de un cáncer y uno o más compuestos adicionales eficaces en el tratamiento del mismo cáncer, donde los compuestos además son eficaces sinérgicamente en el tratamiento del cáncer.

[0191] En algunas realizaciones, la invención proporciona una composición que comprende un compuesto de cualquiera de fórmula (I) y fórmula Ia a fórmula In o un compuesto descrito en este documento, o una sal o solvato del mismo aceptable farmacéuticamente y uno o más agentes. En algunas realizaciones, el o los agentes son seleccionados de un agente alquilante, incluyendo, aunque no taxativamente, adozelesina, altretamina, bendamustina,

bizelesina, busulfano, carboplatina, carboquona, carmofur, carmustina, clorambucil, cisplatina, ciclofosfamida, dacarbacina, estramustina, etoglucida, fotemustina, hepsulfam, ifosfamida, improsulfano, irofulven, lomustina, mannosulfano, mecloretamina, melfalano, mitobronitol, nedaplatina, nimustina, oxaliplatina, piposulfano, prednimustina, procarbacina, ranimustina, satraplatina, semustina, estreptozocina, temozolomida, tiotepa, treosulfano, triaziquona, trietilenomelamina, triplatin tetranitrato, trofosfamida y uramustina; un antibiótico, incluyendo, aunque no taxativamente, aclarubicina, amrubicina, bleomicina, dactinomicina, daunorubicina, doxorubicina, elsamitrucina, epirubicina, idarubicina, menogaril, mitomicina, neocarzinostatina, pentostatina, pirarubicina, plicamicina, valrubicina y zorubicina; un antimetabolito, incluyendo, aunque no taxativamente, aminopterina, azacitidina, azatioprina, capecitabina, cladribina, clofarabina, citarabina, decitabina, floxuridina, fludarabina, 5-fluorouracil, gemcitabina, hidroxiúrea, mercaptopurina, metotrexato, nelarabina, pemetrexed, azatioprina, raltitrexed, tegafur-uracil, tioguanina, trimetoprim, trimetrexato y vidarabina; una inmunoterapia, incluyendo, aunque no taxativamente, alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, panitumumab, pertuzumab, rituximab, tositumomab, trastuzumab, 90 Y ibritumomab tiuxetano, ipilimumab y tremelimumab; una hormona o antagonista de hormona, incluyendo, aunque no taxativamente, anastrozole, andrógenos, buserelina, dietilstilbestrol, exemestano,

flutamida, fulvestrant, goserelina, idoxifeno, letrozole, leuprolida, magestrol, raloxifeno, tamoxifen y toremifeno; a taxano, incluyendo, aunque no taxativamente, DJ-927, docetaxel, TPI 287, larotaxel, ortataxel, paclitaxel, DHA-paclitaxel y tesetaxel; un retinoide, incluyendo, aunque no taxativamente, alitretinoina, bexaroteno, fenretinida, isotretinoina y tretinoina; un alcaloide, incluyendo, aunque no taxativamente, demecolcina, homoharringtonina, vinblastina, vincristina, vindesina, vinflunina y vinorelbina; un agente antiangiogénico, incluyendo, aunque no taxativamente, AE-941 (GW786034, Neovastat), ABT-510, 2-metoxiestradiol, lenalidomida y talidomida; un inhibidor de topoisomerasa, incluyendo, aunque no taxativamente, amsacrina, belotecan, edotecarina, etopósido, etopósido fosfato, exatecano, irinotecano (también metabolito activo SN-38 (7-etil-10-hidroxicamptotecina)), lucantona, mitoxantrona, pixantrona, rubitecán, tenipósido, topotecán y 9-aminocamptotecina; un inhibidor de quinasa, incluyendo, aunque no taxativamente, axitinib (AG 013736), dasatinib (BMS 354825), erlotinib, gefitinib, flavopiridol, imatinib mesilato, lapatinib, motesanib difosfato (AMG 706), nilotinib (AMN107), seliciclib, sorafenib, sunitinib malato, AEE-788, BMS-599626, UCN-01 (7-hidroxistaurosporina) y vatalanib; un inhibidor de transducción de señales seleccionado incluyendo, aunque no taxativamente bortezomib, geldanamicina y Rapamicina; un modificador de la respuesta biológica, incluyendo, aunque no taxativamente, imiquimod, interferon-α e interleu-

quina-2; y otros productos de quimioterapia, incluyendo, aunque no taxativamente 3-AP (3-amino-2-carboxialdehído tiosemicarbazona), altrasentán, aminoglutetimida, anagrelida, asparaginasa, briostatin-1, cilengitida, elesclomol, eribulin mesilato (E7389), ixabepilona, lonidamina, masoprocol, mitoguanazona, oblimersen, sulindac, testolactona, tiazofurin, inhibidores de mTOR (p.ej. temsirolimus, everolimus, deforolimus), inhibidores de PI3K (p.ej. BEZ235, GDC-0941, XL147, XL765), inhibidores de Cdk4 (p.ej. PD-332991), Inhibitors of Akt, inhibidores de Hsp90 (p.ej. tanespimicina) e inhibidores de farnesiltransferasa (p.ej. tipifarnib); inhibidores de MEK (p. ej., AS703026, AZD6244 (selumetinib), AZD8330, BIX02188, CI1040 (PD184352), D-87503, GSK1120212 (JTP-74057), PD0325901, PD318088, PD98059, PDEA119 (BAY 869766), TAK-733). Preferiblemente, el método de tratar un cáncer supone administrar al sujeto una cantidad eficaz de una composición incluyendo cualesquiera uno o más compuesto (s) según se describen en este documento combinado con un agente de quimioterapia seleccionado de capecitabina, 5-fluorouracil, carboplatina, dacarbazina, gefitinib, oxaliplatina, paclitaxel, SN-38, temozolomide, vinblastina, bevacizumab, cetuximab, interferon-β, interleuquina-2 o erlotinib. En algunas realizaciones, un modulador de proteína quinasa, particularmente un compuesto de fórmula (I) a fórmula In, o un compuesto descrito en este documento, o una sal o solvato del mismo aceptable farmacéuticamente, según se define anteriormente, puede ser ad-

ministrado de manera simultánea, secuencial o separada combinado con uno o más agentes según se describe anteriormente.

[0192] En una realización, la invención proporciona métodos para tratar una enfermedad o estado mediado por B-Raf quinasa, incluyendo mutaciones de la misma, administrando al sujeto una cantidad eficaz de una composición incluyendo cualesquiera uno o más compuesto (s) según se describen en este documento combinado con una o más terapias adecuadas adicionales para tratar la enfermedad.

[0193] En una realización, la invención proporciona métodos para tratar una enfermedad o estado mediado por quinasas B-Raf V600 mutantes, como por ejemplo quinasa V600A, V600E, V600G, V600K, V600M o V600R mutante, administrando al sujeto una cantidad eficaz de una composición incluyendo cualesquiera uno o más compuesto (s) según se describen en este documento combinado con uno o más terapias adecuadas adicionales para tratar la enfermedad. En una realización, la invención proporciona métodos para tratar un cáncer mediado por quinasas B-Raf mutantes, como por ejemplo V600A, V600E, V600G, V600M o V600R mutante administrando al sujeto una cantidad eficaz de una composición incluyendo cualesquiera uno o más compuesto (s) según se describe en este documento. En una realización, la invención proporciona métodos para tratar un cáncer mediado por quinasas B-Raf mutantes, como por ejemplo V600A, V600E, V600G, V600K , V600M o V600R mutante administrando al sujeto una cantidad eficaz de una composición

incluyendo cualesquiera uno o más compuesto (s) según se describen en este documento combinado con una o más terapias anticáncer adecuadas, como por ejemplo una o más drogas quimioterapéuticas. En un caso, la quinasa B-Raf mutante es V600A. En otro caso, la quinasa B-Raf mutante es V600E. En otro caso adicional, la quinasa B-Raf mutante es V600G. En otro caso, la quinasa B-Raf mutante es V600K. En otro caso, la quinasa B-Raf mutante es V600M. En otro caso, la quinasa B-Raf mutante es V600R.

[0194] En una realización, la invención proporciona un método para tratar un cáncer en un sujeto que lo necesite administrando al sujeto una cantidad eficaz de una composición incluyendo cualesquiera uno o más compuesto (s) según se describen en este documento combinado con una o más terapias adicionales o procedimientos médicos eficaces en el tratamiento del cáncer. Las terapias adicionales o procedimientos médicos incluyen terapia anticáncer adecuada (p.ej. terapia con fármacos, terapia con vacunas, terapia con genes, terapia fotodinámica) o procedimiento médico (p.ej. cirugía, tratamiento con radiaciones, calentamiento por hipertemia, transplante de células germinales o de médula ósea). En una realización, la o las terapias anticáncer o procedimientos médicos adecuados adicionales se seleccionan del tratamiento con un agente de quimioterapia (p.ej. droga quimioterapéutica), tratamiento con radiaciones (p.ej. rayos X, rayo ϒ o haz de electrones, protones, neutrones o ⍺ partículas), calentamiento por hipertemia (p.ej. microondas, ultrasonido, ablación

por radiofrecuencia), terapia con vacunas (p.ej. vacuna de carcinoma hepatocelular del gen AFP, vacuna del vector adenoviral AFP, AG-858, vacuna alogénica de secreción GM-CSF de cáncer de mama, vacunas de péptidos celulares dendriticos), terapia génica (p.ej. vector Ad5CMV-p53, adenovector que codifica MDA7, factor alfa de necrosis de tumor 5 de adenovirus), terapia fotodinámica (p.ej. ácido aminolevulinico, lutetio motexafina), cirugía o transplante de médula ósea y células germinales.

Equipo

[0195] En otro aspecto, la invención proporciona equipos que incluyen un compuesto de cualquiera de las fórmulas (I) a (In) o un compuesto según se describe en este documento o una composición del mismo según se describe en este documento. En algunas realizaciones, el compuesto o composición es empacado, p. ej., en un vial, botella, frasco, que puede empacarse adicionalmente, p. ej., dentro de una caja, sobre o bolsa; el compuesto o composición está aprobado por el Organismo para el Control de Alimentos y Medicamentos de EE.UU. u organismos reguladores semejantes para la administración a mamíferos, p. ej., un ser humano; el compuesto o composición es aprobado para la administración a u mamífero, p. ej., un ser humano, para una enfermedad o estado mediada por proteína quinasa; el equipo de invención puede incluir instrucciones escritas para el uso y/o indicación que el compuesto o composición es adecuado o aprobado para la administración a mamíferos, p. ej., un ser humano, para una enfermedad

o estado mediado por proteína quinasa Raf; y el compuesto o composición puede estar empacado en forma de dosis unitaria o de dosis sencilla, p. ej., pastillas de una sola dosis, cápsulas, u otros semejantes.

VII. Ejemplos

[0196] Se ofrecen los ejemplos siguientes para ilustrar la invención que se reivindica pero los mismos no son taxativos.

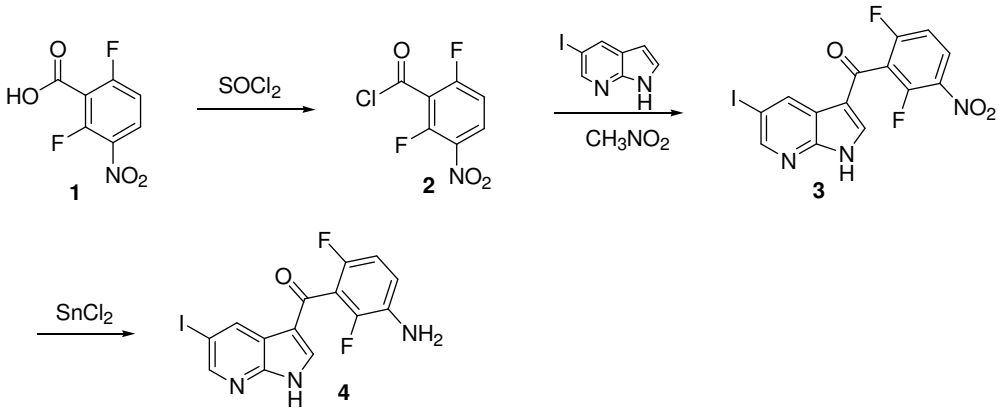
[0197] Los compuestos dentro del alcance de esta invención pueden sintetizarse según se describe más adelante, usando una diversidad de reacciones conocidas entre las personas capacitadas. La persona capacitada en la tecnología también sabrá reconocer que se pueden usar métodos alternativos para sintetizar los compuestos meta de esta invención y que los enfoques descritos dentro del cuerpo de este documento no son exhaustivos pero proporcionan eficazmente rutas prácticas y ampliamente pertinentes a los compuestos de interés. En algunos ejemplos, el resultado de la espectrometría de masas indicada para un compuesto puede tener más de un valor debido a la distribución de isótopos de un átomo en la molécula, como por ejemplo un compuesto que tiene un sustituyente de bromo o de cloro.

[0198] Ciertas moléculas reivindicadas en esta patente pueden existir en diferentes formas enantioméricas y diastereoméricas y todas estas variantes de los compuestos forman parte de las reivindicaciones.

[0199] Las personas capacitadas en la tecnología también sabrán reconocer que durante los procedimientos convencionales de tratamiento final en química orgánica, a menudo se usan ácidos y bases. A veces se producen sales de los compuestos parentales, si poseen la acidez o alcalinidad intrínseca necesaria, durante los procedimientos experimentales descritos dentro de esta patente.

Ejemplo 1: Preparación de (3-Amino-2,6-difluorofenilo)(5-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona (4)

Esquema 1



[0200] Síntesis de 2,6-Difluoro-3-nitrocloruro de benzoilo (2): Se agregó a ácido 2,6-difluoro-3-nitrobenzoico (50 g, 246 mmol) cloruro de tionilo (185 mL, 2536 mmol). Se calentó la reacción a 80 °C de un día para otro y se dejó enfriar hasta temperatura ambiente. Se retiraron los volátiles a presión reducida y seguidamente se realizó azeotropía de tolueno varias veces para producir un aceite el cual se usó directamente en el próximo paso.

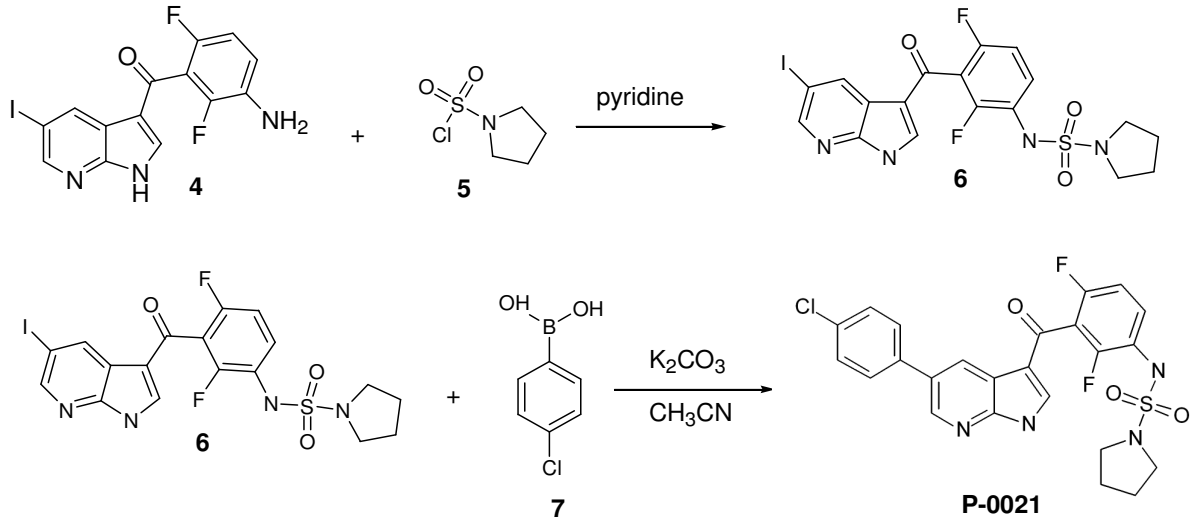
[0201] Síntesis de (2,6-Difluoro-3-nitrofenilo)(5-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona (3): Se mantuvo en agitación 5-Yodo-1H-pirrolo[2,3-b]piridina (32,8 g, 134 mmol) y cloruro de aluminio (108 g, 806 mmol) en nitrometano (340 mL) a temperatura ambiente durante 1 hora. Seguidamente se agregó 2,6-difluoro-3-nitrocloruro de benzoilo (44,7 g, 202 mmol) en nitrometano (340 mL) y la mezcla se calentó a 50 °C durante 5 días. Después de enfriar hasta 0 °C, se mitigó la reacción con metanol (250 mL) lo cual condujo a ppt. Se diluyó la mezcla con agua (500 mL) y seguidamente se filtró. El producto crudo fue triturado con etil acetato y filtrado, lavando con etil acetato adicional para producir (2,6-difluoro-3-nitrofenilo)(5-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona (42 g, 98 mmol, 72,8 % rendimiento) en forma de sólido marrón. El espectro ^{1}H NMR es consistente con la estructura del compuesto.

[0202] Síntesis de (3-Amino-2,6-difluorofenilo)(5-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona (4): A (2,6-difluoro-3-nitrofenilo)(5-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona (44,6 g, 104 mmol) en etil acetato (1732 mL) y THF (1732 mL) se aplicó un tratamiento en forma de gotas con dihidrato de cloruro de estaño (II) (82 g, 364 mmol) mientras se calienta a 60 °C y se mantiene a esta temperatura de un día para otro. Después de enfriar hasta temperatura ambiente, se mitigó la mezcla de reacción con bicarbonato de sodio acuoso medio saturado y filtrado a través de celita lavando la torta con etil acetato. Se separaron

las capas y la capa orgánica fue lavada con salmuera seguidamente se concentró a presión reducida para obtener el producto crudo el cual fue triturado con DCM y filtrado para producir (3-amino-2,6-difluorofenilo)(5-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona (34 g, 85 mmol, 82 % rendimiento) en forma de sólido color tostado. El espectro ^{1}H NMR es consistente con la estructura del compuesto.

Ejemplo 2: N-[3-[5-(4-clorofenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida (P-0021).

Esquema 2



[0203] Síntesis de N-[2,4-difluoro-3-(5-yodo-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]pirrolodina-1-sulfonamida (6): A (3-amino-2,6-difluoro-fenilo)-(5-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona (**4**, 2,9 g, 7,27 mmol) en piridina (11,2 mL), se agregó pirrolodina-1-sulfonilo cloruro (**5**, 1,68 mL, 14,53 mmol). Se agitó la mezcla a temperatura ambiente durante 48 horas. Se

vertió la mezcla obtenida en una solución saturada acuosa de NH_4 Cl y se extrajo con etil acetato. Se combinaron las capas orgánicas y lavaron con salmuera, se secaron con sulfato de sodio anhidroso, seguidamente se procedió a filtrar y concentrar. Se purificó el producto crudo por cromatografía instantánea usando un cartucho de 80 g (eluido con etil acetato y DCM). Se obtuvo el producto deseado en forma de sólido (**6**, 2,06 g, 53,3% rendimiento). MS(ESI) $[M+H^+]^+$ = 532,8. El espectro ^1H NMR es consistente con la estructura del compuesto.

[0204] Síntesis de N-[3-[5-(4-clorofenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida (P-0021): En un recipiente de microondas, se realizó una mezcla de N-[2,4-difluoro-3-(5-yodo-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]pirrolodina-1-sulfonamida (**6**, 0,27g, 0,51 mmol) y ácido (4-clorofenilo)borónico (**7**, 0,1 g, 0,61 mmol) y [1,1'-bis(difenilofosfino)ferroceno]dicloropaladio (II) (27 mg) en 1 M de carbonato de potasio en agua y acetonitrilo (1,31 mL). Se calentó la mezcla a 130 °C en microondas durante 15 minutos. La mezcla obtenida fue separada en una capa orgánica y una capa acuosa. Se extrajo la capa acuosa con etil acetato y se combinaron con la capa orgánica, se lavaron con salmuera, se secaron con sulfato de sodio, seguidamente se procedió a filtrar y concentrar. Se purificó el producto crudo mediante cromatografía usando un cartucho de 40 g (eluido con etil acetato y diclorometano). Se obtuvo un producto purificado en

forma de sólido (P-0021, 0,071 g, 27% rendimiento). El espectro MS (ESI) $[M+H^+]^+$ = 517,0 y 519,0. ^1H NMR es consistente con la estructura del compuesto.

[0205] Se prepararon los compuestos siguientes de conformidad con los protocolos establecidos en los Ejemplos 1, 2 y 4-9 y Esquemas 1, 2 y 4-9.

Tabla 2

5-cloro-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina, **(P-0012)**,

5-(4-clorofenilo)-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0013)**,

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0014)**,

N-[2,4-difluoro-3-(5-fluoro-4-yodo-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]pirrolodina-1-sulfonamida **(P-0015)**,

5-cloro-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0018)**,

5-(4-clorofenilo)-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0019)**,

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0020)**,

N-[3-[5-(4-clorofenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0021)**,

N-[3-[5-[2-(dimetilamino)pirimidin-5-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0022),**

N-[2-fluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]pirrolodina-1-sulfonamida **(P-0023)**

N-[2,4-difluoro-3-(5-yodo-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]pirrolodina-1-sulfonamida **(P-0024),**

3-[3-[[ciclopropilo(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0025),**

[2-fluoro-3-(metilsulfamoilamino)fenilo]-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridin-3-il]metanona **(P-0026),**

5-(4-cianofenilo)-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(0027),**

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-(3-piridilo)-1H-pirrolo[2,3-b]piridina **(P-0028),**

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-(6-metil-3-piridilo)-1H-pirrolo[2,3-b]piridina **(P-0029),**

5-[6-(dimetilamino)-3-piridilo]-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0030),**

5-(4-cianofenilo)-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0031),**

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(3-piridilo)-1H-pirrolo[2,3-b]piridina **(0032),**

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(6-metil-3-piridilo)-1H-pirrolo[2,3-b]piridina **(0033),**

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(4-fluorofenilo)-1H-pirrolo[2,3-b]piridina **(0034),**

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-(4-fluorofenilo)-1H-pirrolo[2,3-b]piridina **(P-0035),**

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-fenilo-1H-pirrolo[2,3-b]piridina **(P-0036),**

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-fenilo-1H-pirrolo[2,3-b]piridina **(P-0037**),

5-bromo-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0038),**

3-[2-fluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina (**P-0040**)

3-bencilooxi-N-[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida (**P-0041**)

1-ciclopropilo-N-[2-fluoro-3-[5-(1-metilpirazol-4-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]metanosulfonamida (**P-0042**)

N-[2-fluoro-3-[5-(3-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida (**P-0043**)

N-[3-[5-(2,4-dimetoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-

sulfonamida (**P-0044**)

N-[2-fluoro-3-[5-(6-metil-3-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida (**P-0045**)

N-[3-[5-[6-(dimetilamino)-3-piridilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida (**P-0046**)

N-[2-fluoro-3-[5-(2-isopropilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida (**P-0047**)

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida (**P-0048**)

N-[3-[5-(4-ciano-3-metoxi-fenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida (**P-0049**)

N-[3-[5-[4-(1-cianociclopropilo)fenilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida (**P-0050**)

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-(2-isopropilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina (**P-0051**)

5-(2-ciclopropilopirimidin-5-il)-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0052**)

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-[6-(trifluorometil)-3-piridilo]-1H-pirrolo[2,3-b]piridina (**P-**

0053)

5-(4-ciano-3-metoxi-fenilo)-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0054**)

5-[4-(1-cianociclopropilo)fenilo]-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0055**)

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-metilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina (**P-0056**)

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-isopropilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina (**P-0057**)

5-(2-ciclopropilopirimidin-5-il)-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0058**)

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-[6-(trifluorometil)-3-piridilo]-1H-pirrolo[2,3-b]piridina (**P-0059**)

5-(4-ciano-3-metoxi-fenilo)-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0060**)

5-[4-(1-cianociclopropilo)fenilo]-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0061**)

N-[2-fluoro-3-[5-(4-fluorofenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida (**P-0062**)

N-[2-fluoro-3-(5-fenilo-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]pirrolodina-1-sulfonamida (**P-0063**)

5-[2-(ciclopropiloamino)pirimidin-5-il]-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0064**)

N-[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]-2-metoxi-etanosulfonamida (**P-0065**)

metil 3-[[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]sulfamoil]propanoato (**P-0066**)

N-[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]ciclopropanosulfonamida (**P-0067**)

[3-(etilsulfamoilamino)-2-fluoro-fenilo]-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridin-3-il]metanona (**P-0068**)

[3-(etilsulfamoilamino)-2-fluoro-fenilo]-(5-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona (**P-0069**)

3-[2-fluoro-3-[[isobutil(metil)sulfamoil]amino]benzoil]-5-yodo-1H-pirrolo[2,3-b]piridina (**P-0070**)

[2-fluoro-3-(isopropilsulfamoilamino)fenilo]-(5-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona (**P-0071**)

3-[2-fluoro-3-[[isobutil(metil)sulfamoil]amino]benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina (**P-0072**)

3-[2-fluoro-3-[[2-metoxietil(metil)sulfamoil]amino]benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina (**P-0073**)

N-[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]-2-metil-pirrolodina-1-sulfonamida (**P-0074**)

3-[2-fluoro-3-[[isopropil(metil)sulfamoil]amino]benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina (**P-0075**)

5-[6-(dimetilamino)-3-piridilo]-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0076**)

5-[2-(ciclopropiloamino)pirimidin-5-il]-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0077**)

5-(2-ciclopropilopirimidin-5-il)-3-[2,6-difluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina (**P-0078**)

5-[4-(1-cianociclopropilo)fenilo]-3-[2,6-difluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina (**P-0079**)

5-[4-(1-cianociclopropilo)fenilo]-3-[2-fluoro-3-[[2-metoxietil(metil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina (**P-0080**)

5-[2-(ciclopropiloamino)pirimidin-5-il]-3-[2-fluoro-3-[[2-metoxietil(metil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-

b]piridina (**P-0081**)

5-[2-(ciclopropiloamino)pirimidin-5-il]-3-[2-fluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina (**P-0082**)

3-[3-[[ciclopropilometilo(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina (**P-0083**)

3-[3-[[ciclopropilometilo(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina (**P-0084**)

5-(2-ciclopropilopirimidin-5-il)-3-[2-fluoro-3-[[2-metoxietil(metil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina (**P-0085**)

5-(2-ciclopropilopirimidin-5-il)-3-[2-fluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina (**P-0086**)

5-(6-ciclopropilo-3-piridilo)-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0087**)

3,3-difluoro-N-[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]acetidina-1-sulfonamida (**P-0088**)

4-[[(1S)-1-ciclopropiloetil]amino]-5-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-7H-

pirrolo[2,3-d]pirimidina (**P-0089**)

N-[3-[5-(4-cianofenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida (**P-0090**)

N-[3-[5-(2-cianopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida (**P-0091**)

N-[2-fluoro-3-[5-(2-metilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida (**P-0092**)

N-[3-[5-(5-ciano-3-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida (**P-0093**)

N-[3-[5-(6-ciano-3-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida (**P-0094**)

N-[2-fluoro-3-[5-[6-(trifluorometil)-3-piridilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida (**P-0095**)

5-(2-cianopirimidin-5-il)-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0096**)

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-(2-metilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina (**P-0097**)

5-(5-ciano-3-piridilo)-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0098**)

5-(6-ciano-3-piridilo)-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0099**)

5-(2-cianopirimidin-5-il)-3-[3-[[etil(metil)sulfamoil]amino]-

2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0100**)

5-(5-ciano-3-piridilo)-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0101**)

5-(6-ciano-3-piridilo)-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0102**)

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-[4-(1-hidroxi-1-metil-etil)fenilo]-1H-pirrolo[2,3-b]piridina (**P-0103**)

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-[4-(1-hidroxi-1-metil-etil)fenilo]-1H-pirrolo[2,3-b]piridina (**P-0104**)

N-[2-fluoro-3-[5-[4-(1-hidroxi-1-metil-etil)fenilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida (**P-0105**)

5-[2-(dimetilamino)pirimidin-5-il]-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0106**)

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-(2-pirrolidin-1-ilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina (**P-0107**)

3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-pirrolidin-1-ilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina (**P-0108**)

N-[2-fluoro-3-[5-(2-pirrolidin-1-ilpirimidin-5-il)-1H-

pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida (**P-0109**)

3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-5-yodo-1H-pirrolo[2,3-b]piridina (**P-0110**)

3-[2-fluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-5-(2-metilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina (**P-0111**)

3-[3-[[ciclopropilometilo(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-metilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina (**P-0112**)

5-(6-ciclopropilo-3-piridilo)-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina (**P-0113**)

5-(6-ciclopropilo-3-piridilo)-3-[2-fluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina (**P-0114**)

3-[3-[[ciclopropilometilo(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(6-ciclopropilo-3-piridilo)-1H-pirrolo[2,3-b]piridina (**P-0115**)

3-[2,6-difluoro-3-[[metil(propil)sulfamoil]amino]benzoil]-5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina (**P-0116**)

[2-fluoro-3-(propilsulfamoilamino)fenilo]-(5-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona (**P-0117**)

[2-fluoro-3-(propilsulfamoilamino)fenilo]-(5-metil-1H-pirrolo[2,3-b]piridin-3-il)metanona **(P-0223)**

N-[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]butano-2-sulfonamida **(P-0224)**

N-[2-fluoro-3-[5-(2-pirrolidin-1-ilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]butano-2-sulfonamida **(P-0225)**

N-[3-[5-[2-(ciclopropiloamino)pirimidin-5-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]butano-2-sulfonamida **(P-0226)**

N-[3-[5-[4-(1-cianociclopropilo)fenilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]butano-2-sulfonamida **(P-00227)**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]butano-2-sulfonamida **(P-0228)**

N-[2-fluoro-3-[5-(2-isopropilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]butano-2-sulfonamida **(P-0229)**

N-[3-[5-[6-(dimetilamino)-3-piridilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]butano-2-sulfonamida **(P-0230)**

N-[2-fluoro-3-[5-(2-metilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]butano-2-sulfonamida **(P-0231)**

N-[3-[5-[2-(ciclopropiloamino)pirimidin-5-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0232)**

5-(2-ciclopropilopirimidin-5-il)-3-[2-fluoro-3-[[isopropil(metil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina **(P-0233)**

N-[2-fluoro-3-[5-(2-morfolinopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0235)**

N-[2-fluoro-3-[5-(2-morfolinopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]butano-2-sulfonamida **(P-0236)**

5-[4-(1-cianociclopropilo)fenilo]-3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0237)**

5-(2-ciclopropilopirimidin-5-il)-3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0238)**

5-[4-(1-cianociclopropilo)fenilo]-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0239)**

5-(2-ciclopropilopirimidin-5-il)-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0240)**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0241)**

[2-fluoro-3-(propilsulfamoilamino)fenilo]-[5-(1-metilpirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-il]metanona **(P-0242)**

1-[4-[3-[2-fluoro-3-(pirrolidin-1-ilsulfonilamino)benzoil]-1H-

pirrolo[2,3-b]piridin-5-il]fenilo]ciclopropano ácido carboxílico **(P-0243)**

3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-5-(5-etoxipiracin-2-il)-1H-pirrolo[2,3-b]piridina **(P-0244)**

5-[4-(1-ciano-1-metil-etil)fenilo]-3-[3-(dimetilsulfamoilamino)-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0245)**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]-3,3-dimetil-pirrolodina-1-sulfonamida **(P-0246)**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]-3-metil-pirrolodina-1-sulfonamida **(P-0247);**

N-[3-[5-[4-(1-cianociclopropilo)fenilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0248)**

3-[3-[[ciclopropilo(metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0249)**

[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridin-3-il]-[2-fluoro-3-(propilsulfamoilamino)fenilo]metanona **(P-0251)**

3-[3-[[ciclopropilo(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0252)**

1-[4-[3-[2-fluoro-3-(pirrolidin-1-ilsulfonilamino)benzoil]-1H-pirrolo[2,3-b]piridin-5-il]fenilo]ciclopropanocarboxamida **(P-0253)**

metil 1-[4-[3-[2-fluoro-3-(pirrolidin-1-ilsulfonilamino)benzoil]-1H-pirrolo[2,3-b]piridin-5-il]fenilo]ciclopropanocarboxilato **(P-0254)**

5-[4-(1-ciano-1-metil-etil)fenilo]-3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0255)**

5-(2-etoxipirimidin-5-il)-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0256)**

etil 1-[[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]sulfamoil]pirrolodina-2-carboxilato **(P-0257)**

4-[5-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]pirimidin-2-il]morfolina **(P-0258)**

4-[3-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]fenilo]morfolina **(P-0259)**

N-[2,4-difluoro-3-[5-[2-(4-metilpiperacin-1-il)pirimidin-5-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0260)**

N-[2,4-difluoro-3-[5-(2-piperacin-1-ilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0261)**

N-[2,4-difluoro-3-[5-[2-(4-hidroxi-1-piperidil)pirimidin-5-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0262)**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-[2-(4-metilpiperacin-1-il)pirimidin-5-il]-1H-pirrolo[2,3-b]piridina **(P-0263)**

terc-butil 4-[5-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]pirimidin-2-il]piperacina-1-carboxilato **(P-0264)**

N-[2,4-difluoro-3-[5-[2-(1-hidroxi-1-metil-etil)tiazol-4-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0265)**

N-[2,4-difluoro-3-[5-(2-morfolinopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0266)**

N-[1-[[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]sulfamoil]pirrolidin-3-il]-N-metil-acetamida **(P-0267)**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(2-piperacin-1-ilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0268)**

N-[3-[5-[2-(azetidin-1-il)pirimidin-5-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0269)**

N-[2,4-difluoro-3-[5-(2-metoxitiazol-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0270)**

(3R)-N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]-3-metil-pirrolodina-1-sulfonamida **(P-0271)**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]-3-(metilamino)pirrolodina-1-sulfonamida **(P-0272)**

N-[2,4-difluoro-3-[5-(4-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0273)**

N-[3-(5-ciclopropilo-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0274)**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-[2-(4-hidroxi-1-piperidil)pirimidin-5-il]-1H-pirrolo[2,3-b]piridina **(P-0275)**

5-[3-(1-cianociclopropilo)fenilo]-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0276)**

5-[2-(azetidin-1-il)pirimidin-5-il]-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0277)**

N-[3-[5-(2-aminopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-**

0279)

N-[3-[5-(2-aminopirimidin-4-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0280)**

N-[2-fluoro-3-[5-(4-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0281)**

N-[2,4-difluoro-3-[5-(2-morfolinopirimidin-4-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0282)**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(2-fluoro-4-piridilo)-1H-pirrolo[2,3-b]piridina **(P-0283)**

N-[2,4-difluoro-3-[5-(2-morfolino-4-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0284)**

N-[2,4-difluoro-3-[5-[2-(4-metilpiperacin-1-il)-4-piridilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0285)**

N-[3-[5-[2-(ciclobutoxi)-4-piridilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0286)**

N-[2,4-difluoro-3-[5-(2-metoxi-4-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0287)**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-

b]piridina-3-carbonilo]-2,4-difluoro-fenilo]-3,3-difluoro-pirrolodina-1-sulfonamida **(P-0288)**

(3S)-N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]-3-fluoro-pirrolodina-1-sulfonamida **(P-0289)**

metil 2-[[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]sulfamoil]propanoato **(P-0291)**

5-[2-(dimetilamino)pirimidin-5-il]-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0292)**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(2-pirrolidin-1-ilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina **(P-0293)**

N-[2,4-difluoro-3-[5-[6-(trifluorometil)pirimidin-4-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0294)**

N-[3-[5-(2-ciclopropilo-4-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida **(P-0295)**

5-ciclobutilo-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0297)**

5-ciclopropilo-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0298)**

N-[3-[5-(6-aminopirimidin-4-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0299)**

5-(4-cianofenilo)-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0300)**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-[4-(trifluorometil)fenilo]-1H-pirrolo[2,3-b]piridina **(P-0301)**

5-[3-(dimetilamino)fenilo]-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0302)**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(4-pirrolidin-1-ilfenilo)-1H-pirrolo[2,3-b]piridina **(P-0303)**

2-[4-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]fenilo]-5-metil-1,3,4-oxadiazole **(P-0304)**

2-[4-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]fenilo]-5-(metilamino)-1,3,4-tiadiazole **(P-0305)**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-[5-(1-hidroxi-1-metil-etil)-3-piridilo]-1H-pirrolo[2,3-b]piridina **(P-0306)**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-[6-(1-hidroxi-1-metil-etil)-3-piridilo]-1H-pirrolo[2,3-b]piridina **(P-0307)**

5-[4-(dietilamino)fenilo]-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0308)**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(2-oxoindolin-6-il)-1H-pirrolo[2,3-b]piridina **(P-0309)**

3-[5-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]-2-tienilo]-5-metil-1,2,4-oxadiazole **(P-0310)**

2-amino-6-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]quinazolina **(P-0311)**

N-ciclopropilo-5-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]piridina-2-carboxamida **(P-0312)**

2-(dimetilamino)-6-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]quinazolina **(P-0313)**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-[4-(1-hidroxiciclopropilo)fenilo]-1H-pirrolo[2,3-b]piridina **(P-0314)**

5-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]tiazole **(P-0315)**

4-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]-2-(1-hidroxi-1-metil-etil)tiazole **(P-0316)**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(6-metoxipiridazin-3-il)-1H-pirrolo[2,3-b]piridina **(P-0317)**

N-[2,4-difluoro-3-[5-(6-morfolinopirimidin-4-il)-1H-

pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0318)**

N-[2,4-difluoro-3-[5-[6-(4-metilpiperacin-1-il)pirimidin-4-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0319)**

(3S)-N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]-3-metil-pirrolodina-1-sulfonamida **(P-0320)**

N-[2-fluoro-3-[5-(6-morfolinopirimidin-4-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0321)**

N-[2-fluoro-3-[5-[6-(4-metilpiperacin-1-il)pirimidin-4-il]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0322)**

N-[2-fluoro-3-[5-[6-(4-metilpiperacin-1-il)-2-piridilo]-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0324)**

N-[2-fluoro-3-[5-(4-metoxipirimidin-2-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0325)**

N-[2-fluoro-3-[5-(4-metilpirimidin-2-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0326)**

(3R)-N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-

b]piridina-3-carbonilo]-2-fluoro-fenilo]-3-fluoro-pirrolodina-1-sulfonamida **(P-0327)**

[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridin-3-il]-[2,6-difluoro-3-(metilsulfamoilamino)fenilo]metanona **(P-0334)**

[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridin-3-il]-[3-(etilsulfamoilamino)-2,6-difluoro-fenilo]metanona **(P-0335)**

5-(2-ciclopropilopirimidin-5-il)-3-[2,6-difluoro-3-(sulfamoilamino)benzoil]-1H-pirrolo[2,3-b]piridina **(P-0336)**

N-[3-[5-(4-clorofenilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]butano-2-sulfonamida **(P-0337)**

(3R)-N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]-3-fluoro-pirrolodina-1-sulfonamida **(P-0338)**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]-3-fluoro-pirrolodina-1-sulfonamida **(P-0339)**

5-(2-ciclopropilopirimidin-5-il)-3-[2,6-difluoro-3-[[metil(2,2,2-trifluoroetil)sulfamoil]amino]benzoil]-1H-pirrolo[2,3-b]piridina **(P-0340)**

N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]butano-2-sulfonamida **(P-0342)**

5-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridin-5-il]-2-metoxi-tiazole **(P-0343)**

3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(1H-indazol-6-il)-1H-pirrolo[2,3-b]piridina **(P-0344)**

N-[2,4-difluoro-3-[5-(2-pirrolidin-1-ilpirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]pirrolodina-1-sulfonamida **(P-0345)**

N-[3-(5-ciclobutilo-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-fenilo]pirrolodina-1-sulfonamida **(P-0346)**

N-[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]ciclopropanosulfonamida **(P-0347)**

1-alilo-N-[3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]ciclopropanosulfonamida **(P-0348)**

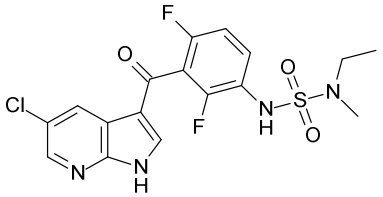
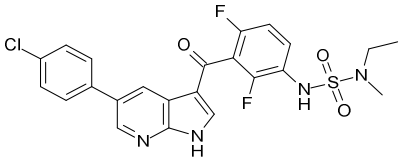
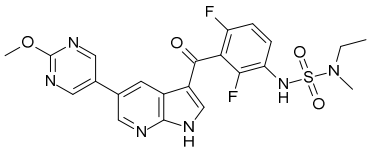
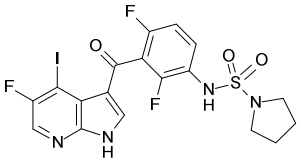
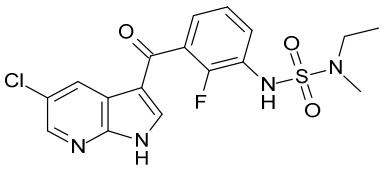
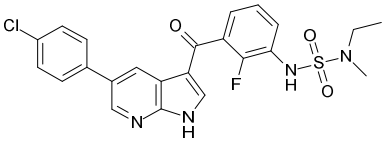
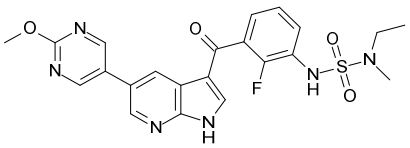
N-[2,4-difluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]ciclopropanosulfonamida **(P-0349)**

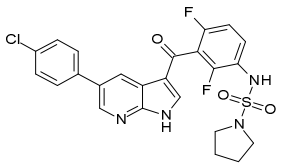
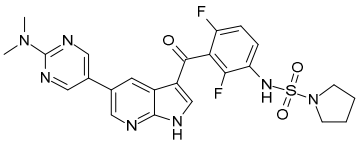
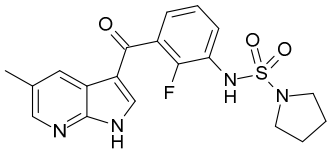
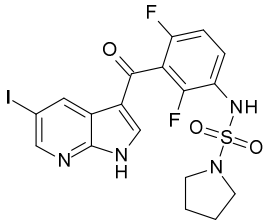
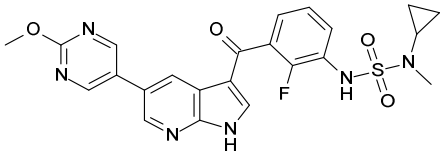
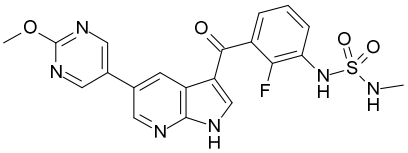
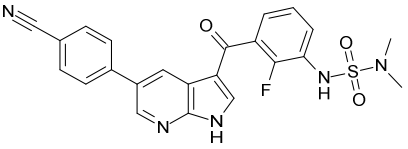
N-[2,4-difluoro-3-[5-(5-metoxi-3-piridilo)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]ciclopropanosulfonamida **(P-0350)**

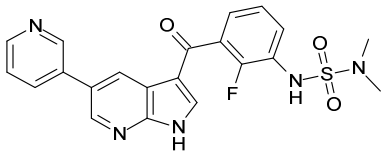
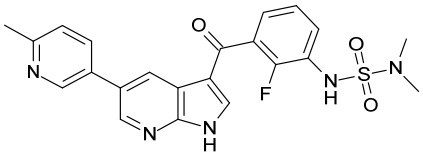
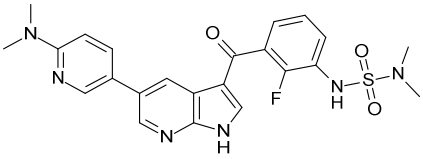
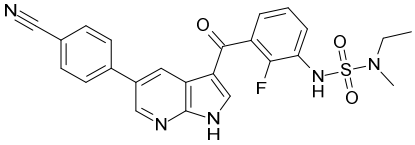
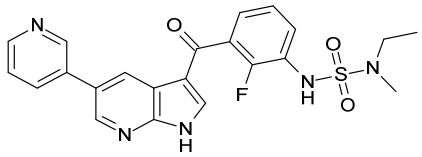
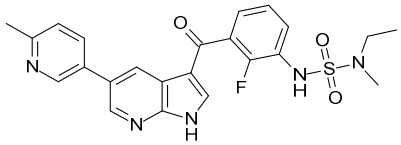
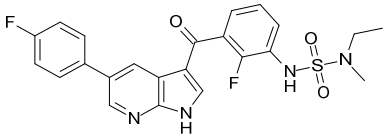
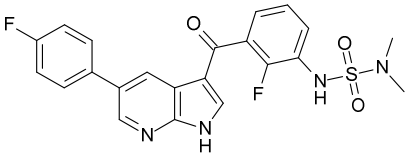
N-[3-(5-ciano-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]ciclopropanosulfonamida **(P-0351)**

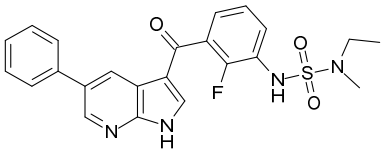
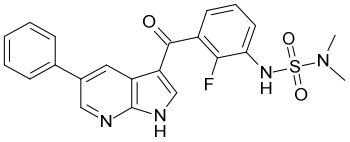
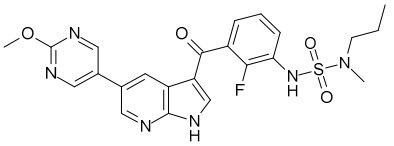
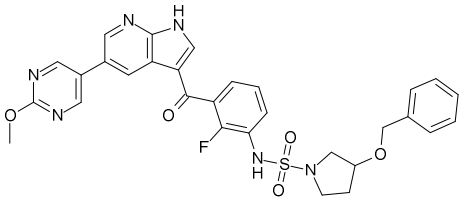
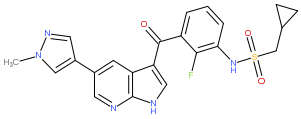
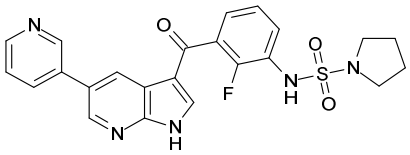
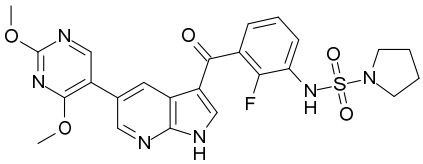
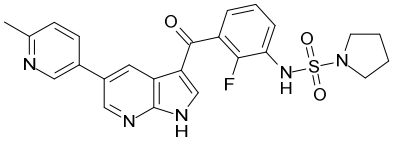
La tabla siguiente proporciona estructuras de ciertos compuestos de la presente invención y la masa observada. Los espectros ^{1}H NMR fueron consistentes con las estructuras de los compuestos.

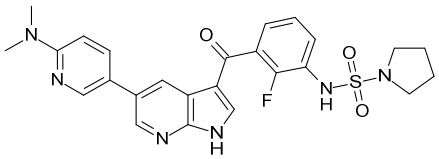
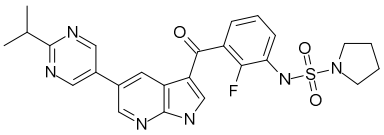
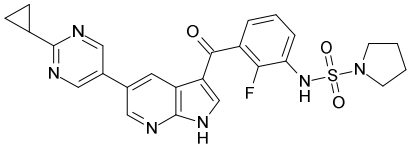
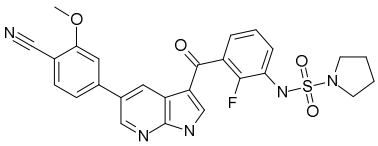
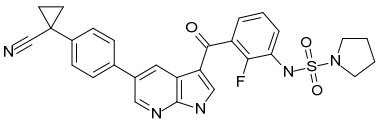
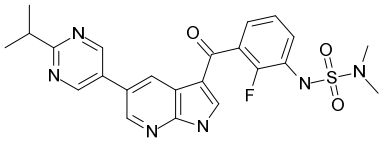
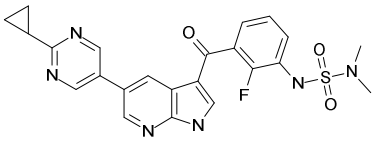
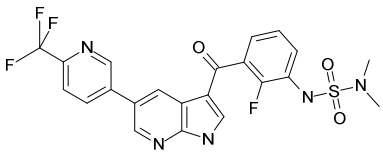
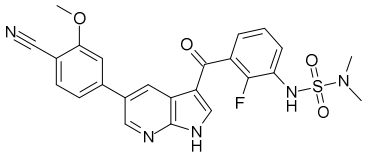
No.	Compuestos	MS(ESI) $[M+H^+]^+$ observada

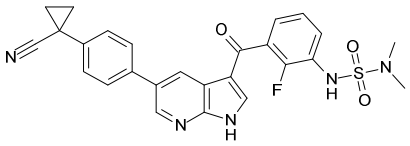
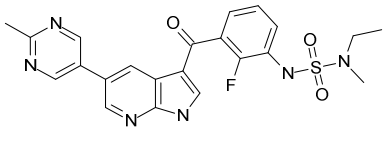
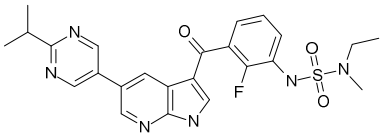
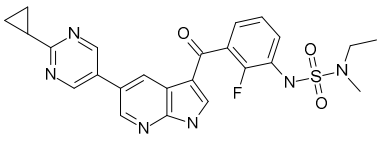
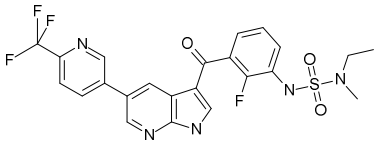
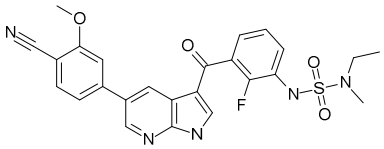
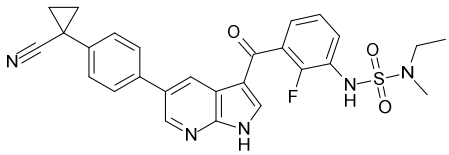
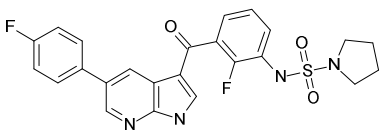
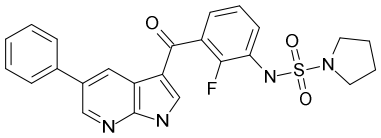
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P-0015		551,1
P-0018		410,9
P-0019		489,0
P-0020		485,1

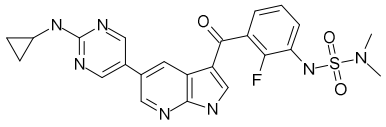
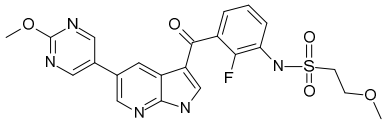
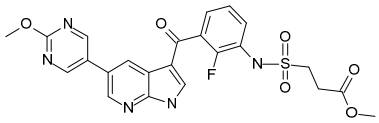
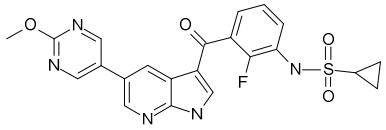
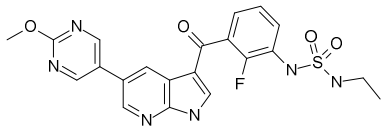
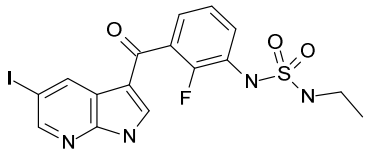
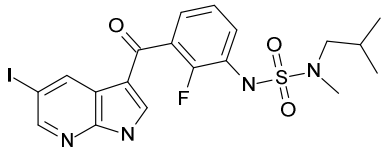
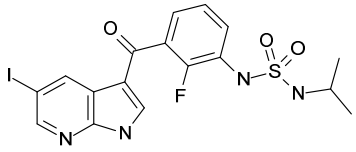
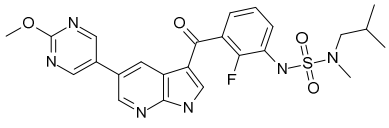
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P-0025		497,0
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P-0027		463,5

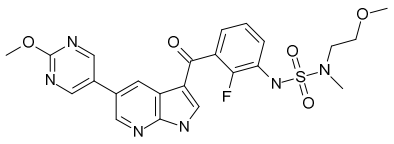
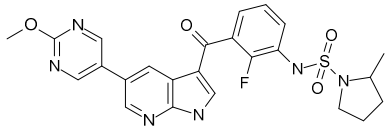
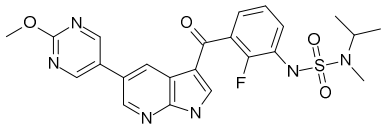
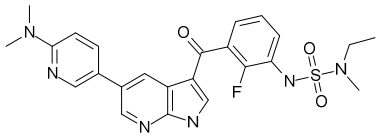
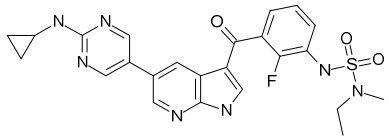
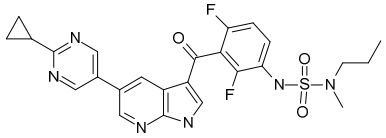
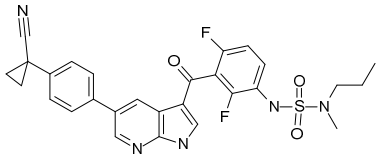
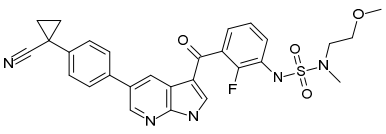
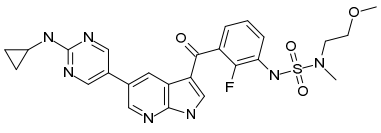
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P-0031		478,5
P-0032		454,5
P-0033		468,2
P-0034		471,5
P-0035		457,5

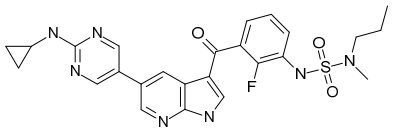
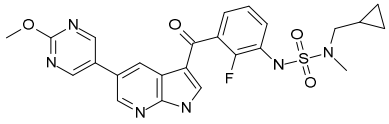
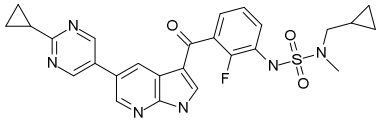
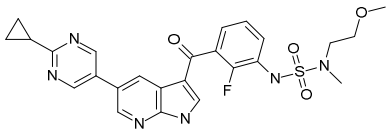
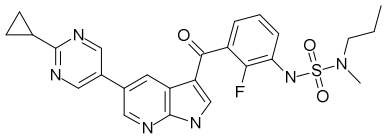
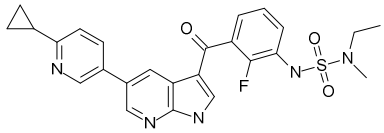
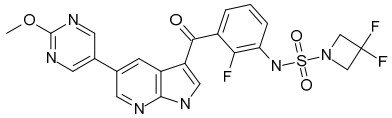
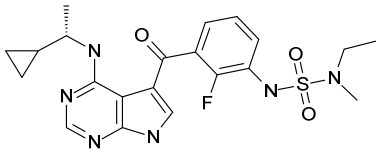
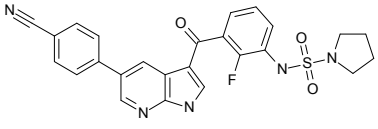
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P-0037		439,2
P-0040		499,0
P-0041		603,6
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P-0043		466,0
P-0044		427,5
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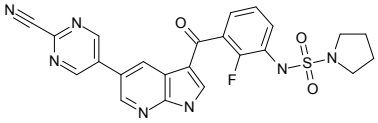
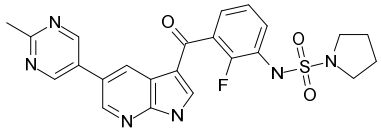
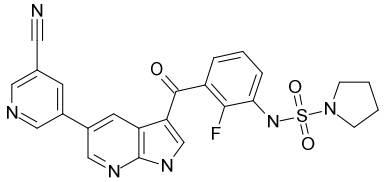
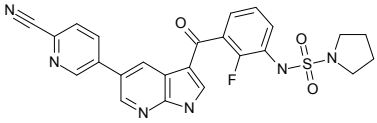
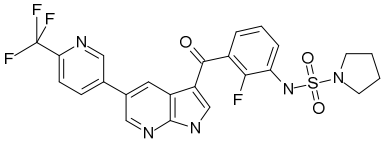
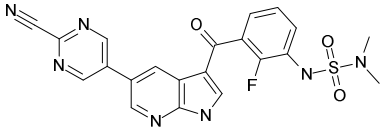
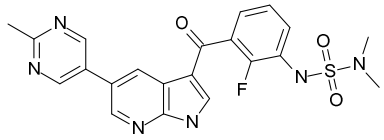
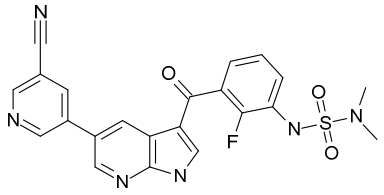
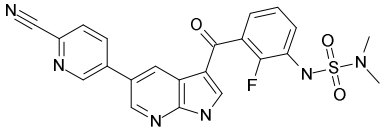
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P-0048		507,0
P-0049		520,0
P-0050		530,0
P-0051		483,1
P-0052		481,0
P-0053		508,0
P-0054		494,0

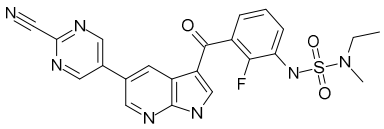
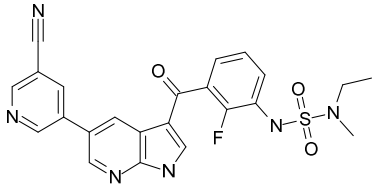
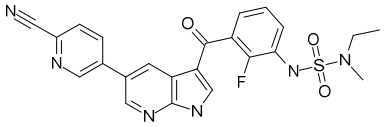
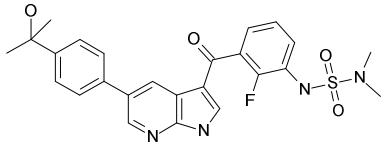
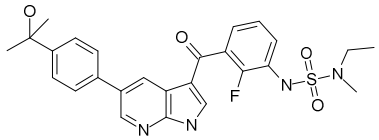
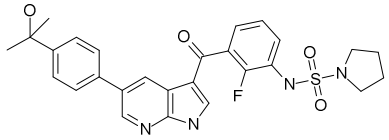
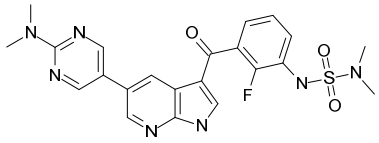
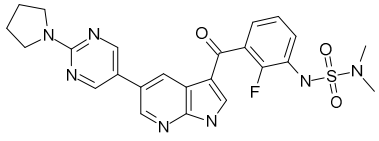
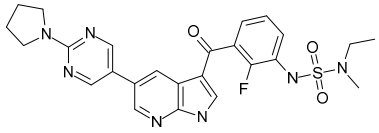
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P-0056		469,0
P-0057		497,0
P-0058		495,0
P-0059		522,0
P-0060		508,0
P-0061		518,1
P-0062		483,0
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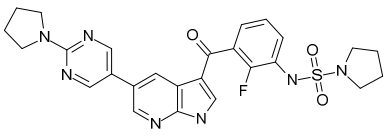
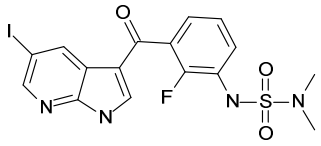
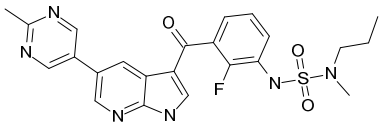
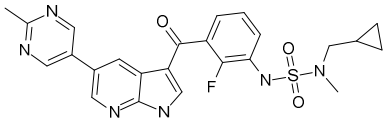
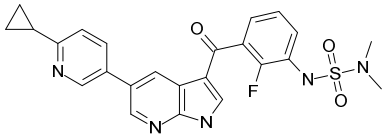
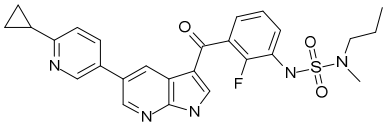
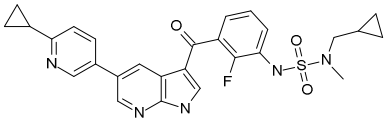
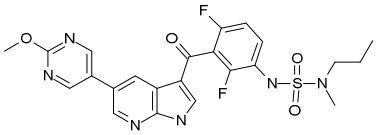
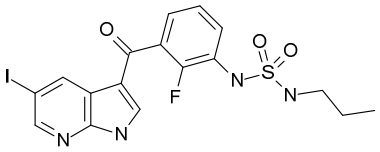
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P-0065		486,0
P-0066		514,0
P-0067		468,0
P-0068		471,0
P-0069		489,0
P-0070		499,0
P-0071		503,1
P-0072		513,5

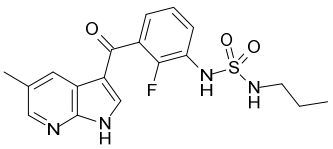
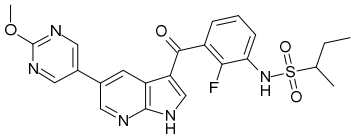
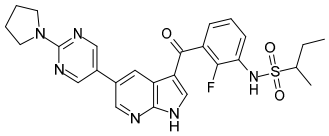
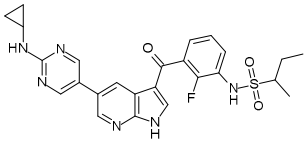
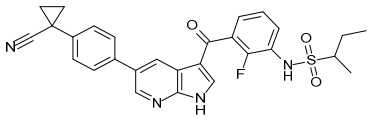
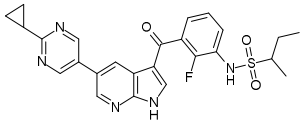
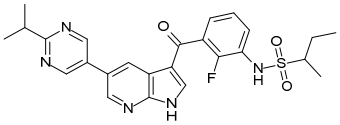
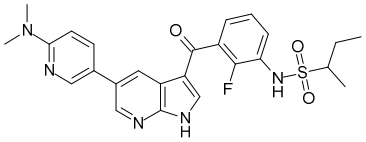
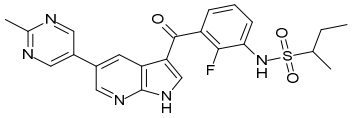
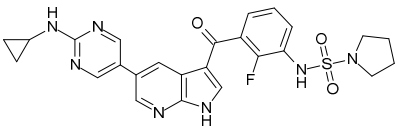
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P-0074		511,0
P-0075		499,0
P-0076		497,1
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P-0078		527,1
P-0079		550,0
P-0080		548,0
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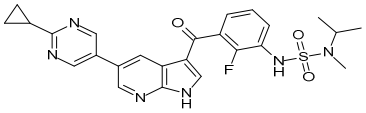
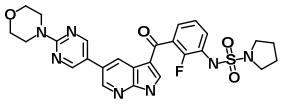
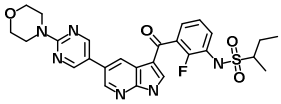
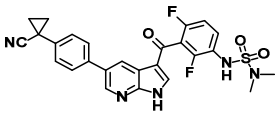
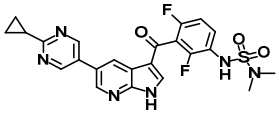
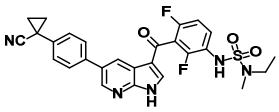
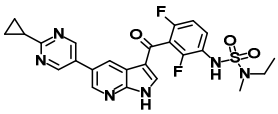
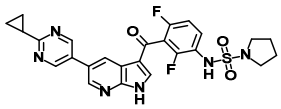
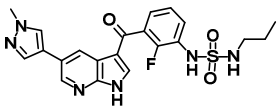
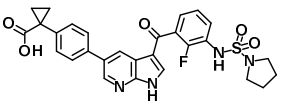
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P-0083		511,1
P-0084		521,1
P-0085		525,1
P-0086		509,1
P-0087		494,2
P-0088		519,5
P-0089		461,1
P-0090		490,5

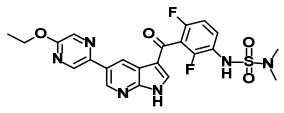
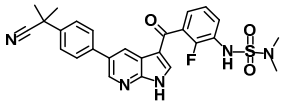
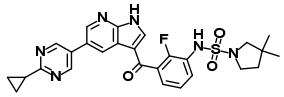
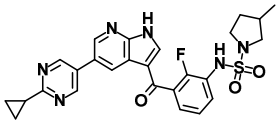
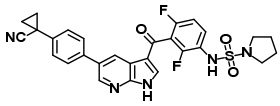
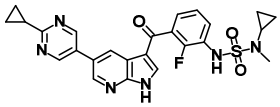
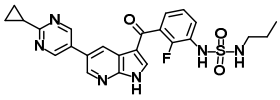
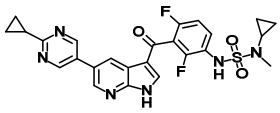
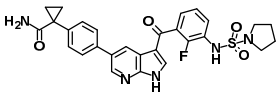
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P-0092		481,5
P-0093		491,5
P-0094		491,5
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P-0096		466,5
P-0097		455,5
P-0098		465,4
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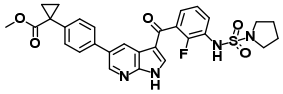
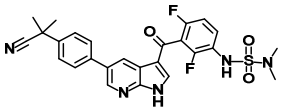
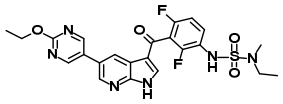
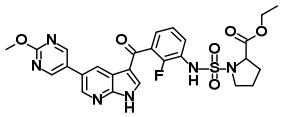
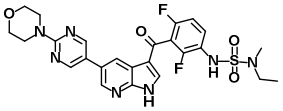
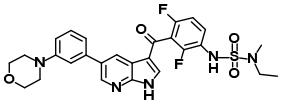
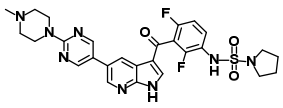
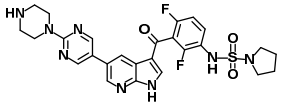
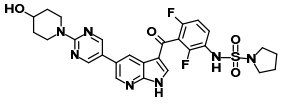
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P-0101		479,5
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P-0103		497,5
P-0104		511,6
P-0105		523,6
P-0106		484,5
P-0107		510,6
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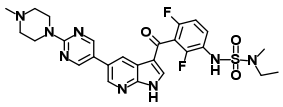
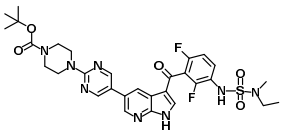
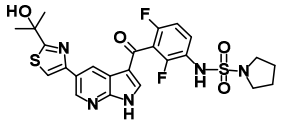
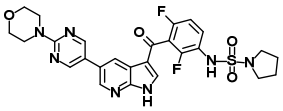
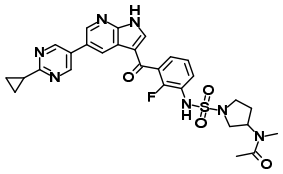
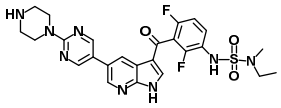
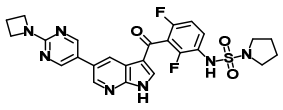
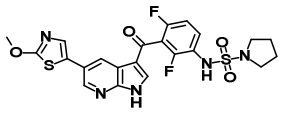
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P-0110		489,3
P-0111		483,5
P-0112		495,5
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P-0114		508,6
P-0115		520,6
P-0116		517,5
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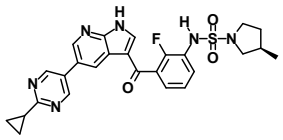
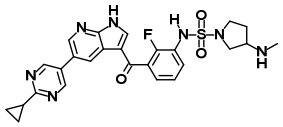
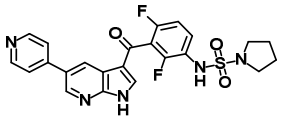
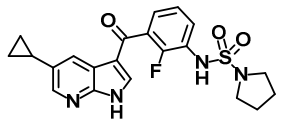
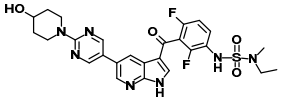
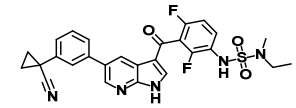
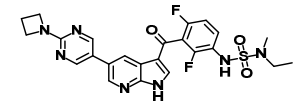
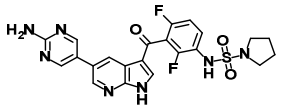
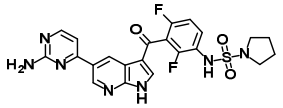
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P-0224		484,5
P-0225		523,6
P-0226		509,6
P-0227		517,6
P-0228		4946
P-0229		496,6
P-0230		496,6
P-0231		468,6
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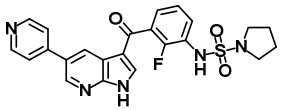
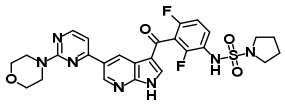
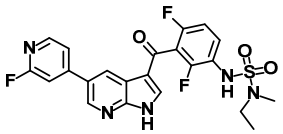
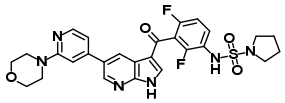
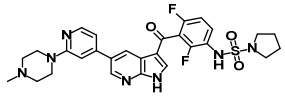
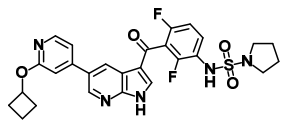
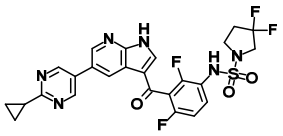
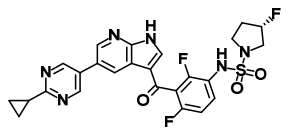
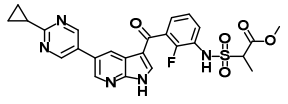
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P-0235		552,5
P-0236		539,4
P-0237		522,5
P-0238		499,5
P-0239		536,6
P-0240		513,5
P-0241		525,2
P-0242		457,5
P-0243		549,6

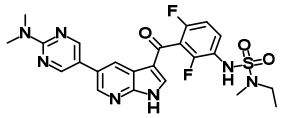
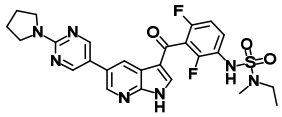
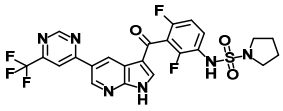
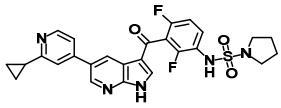
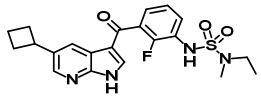
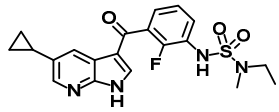
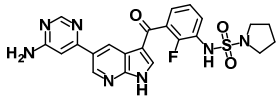
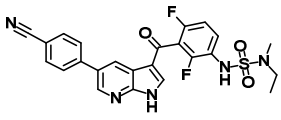
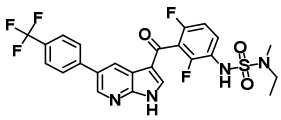
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P-0245		506,4
P-0246		535,6
P-0247		521,5
P-0248		548,5
P-0249		507,5
P-0251		495,5
P-0252		525,5
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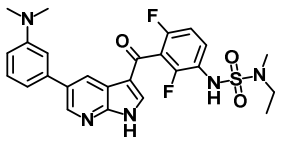
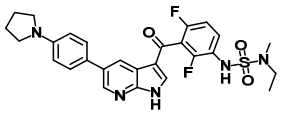
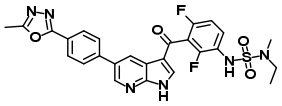
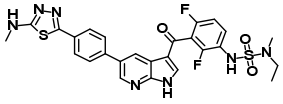
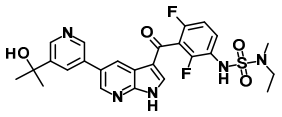
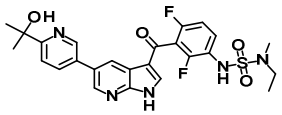
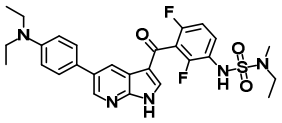
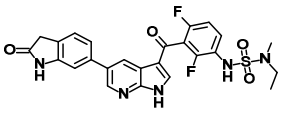
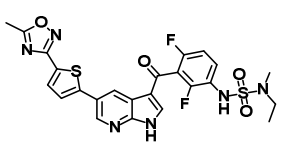
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P-0255		524,5
P-0256		517,2
P-0257		569,6
P-0258		558,5
P-0259		556,6
P-0260		583,6
P-0261		569,4
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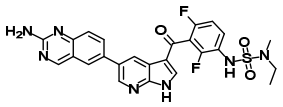
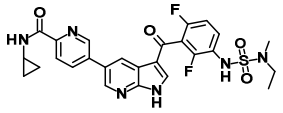
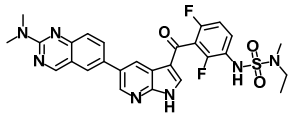
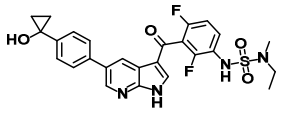
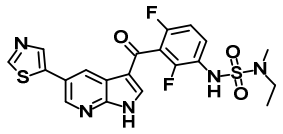
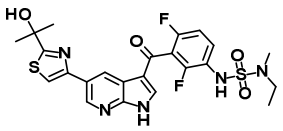
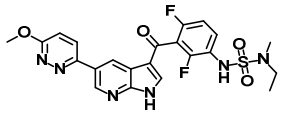
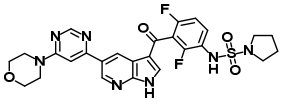
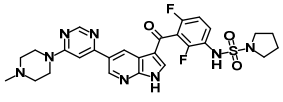
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P-0264		657,7
P-0265		548,6
P-0266		570,5
P-0267		578,6
P-0268		557,5
P-0269		540,5
P-0270		520,6

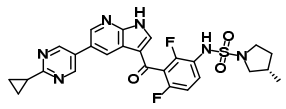
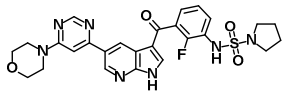
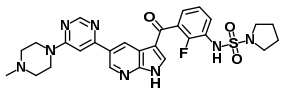
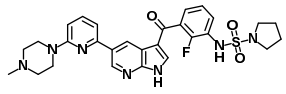
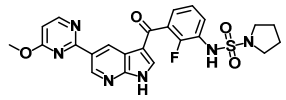
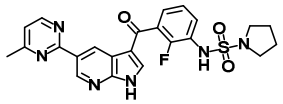
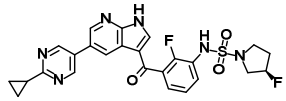
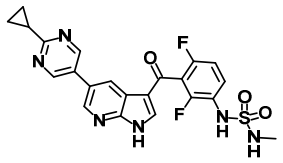
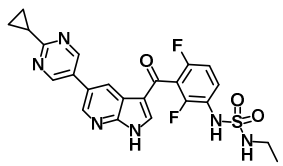
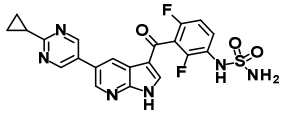
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P-0272		536,6
P-0273		484,4
P-0274		429,4
P-0275		572,6
P-0276		536,5
P-0277		528,5
P-0279		500,3
P-0280		500,5

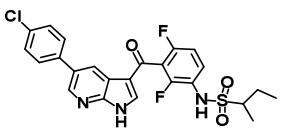
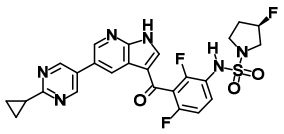
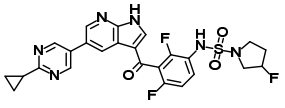
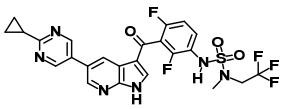
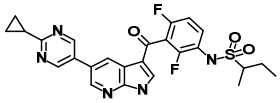
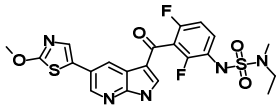
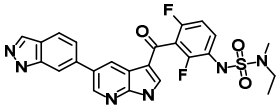
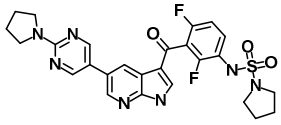
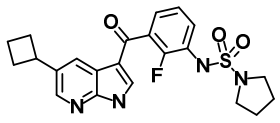
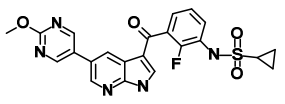
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P-0282		570,6
P-0283		490,4
P-0284		569,6
P-0285		582,5
P-0286		554,6
P-0287		514,5
P-0288		561,5
P-0289		543,4
P-0291		524,2

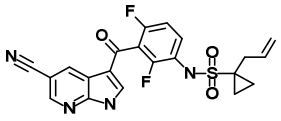
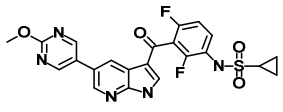
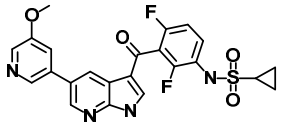
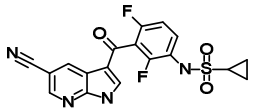
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P-0293		542,5
P-0294		553,5
P-0295		524,6
P-0297		431,5
P-0298		417,4
P-0299		482,5
P-0300		496,5
P-0301		539,4

P-0302		514,6
P-0303		540,5
P-0304		553,6
P-0305		584,6
P-0306		530,5
P-0307		530,2
P-0308		542,5
P-0309		526,5
P-0310		559,5

P-0311		538,5
P-0312		555,4
P-0313		566,6
P-0314		527,5
P-0315		478,5
P-0316		536,0
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P-0318		570,5
P-0319		583,6

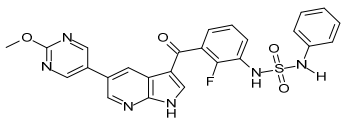
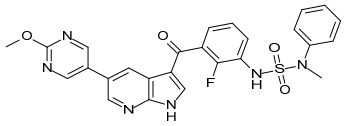
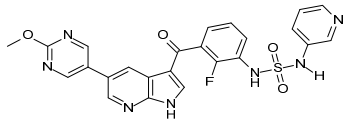
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P-0321		552,5
P-0322		565,5
P-0324		564,8
P-0325		497,5
P-0326		481,4
P-0327		525,5
P-0334		485,4
P-0335		499,5
P-0336		471,4

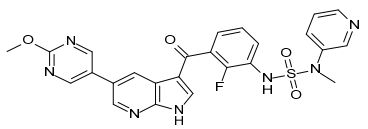
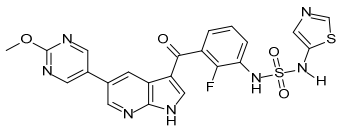
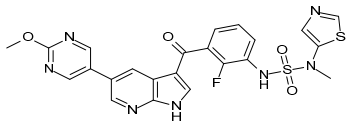
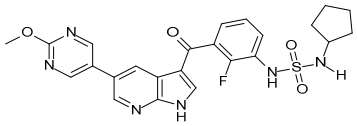
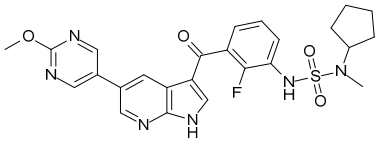
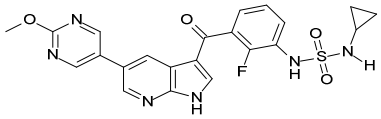
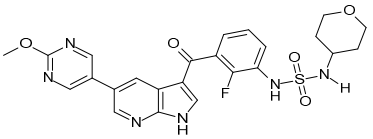
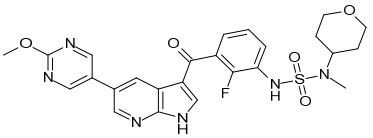
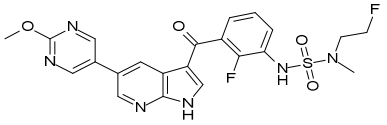
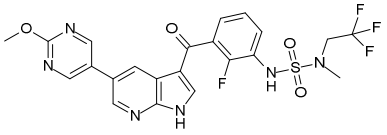
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P-0338		542,9
P-0339		543,5
P-0340		567,5
P-0342		512,5
P-0343		507,5401
P-0344		511,5
P-0345		554,6
P-0346		443,5
P-0347		468,4

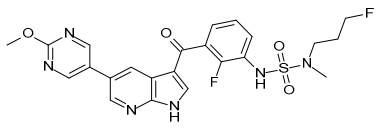
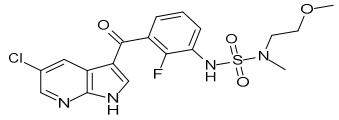
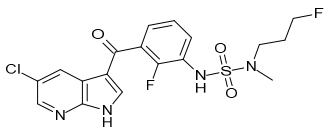
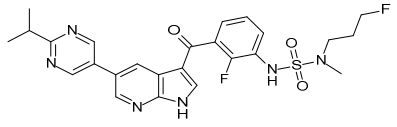
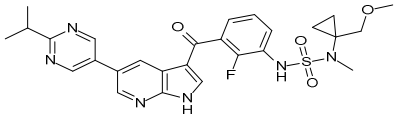
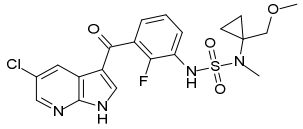
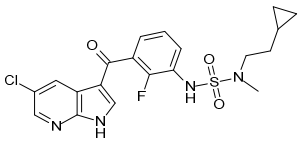
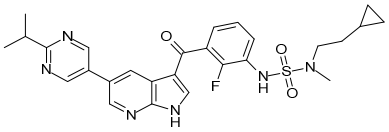
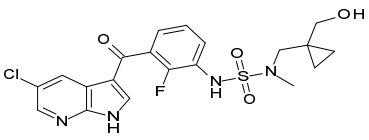
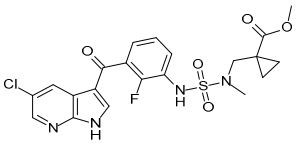
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P-0350		485,5
P-0351		403,3

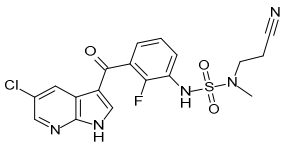
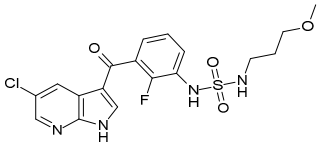
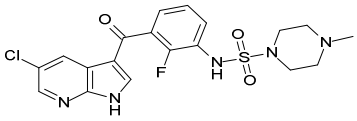
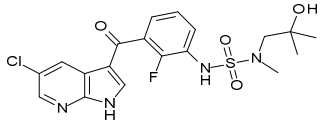
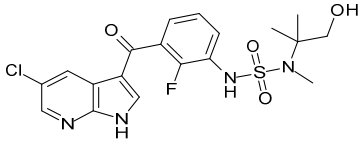
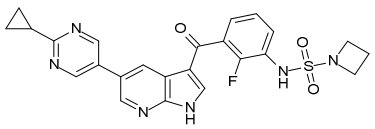
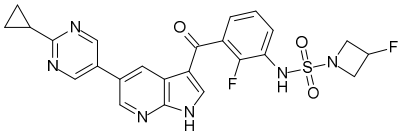
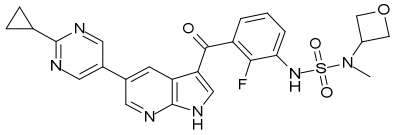
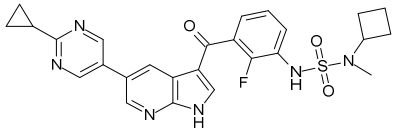
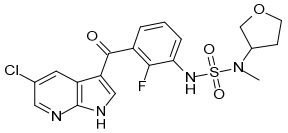
[0206] Los compuestos siguientes también son preparados de conformidad con los protocolos establecidos en los Ejemplos 1, 2 y 4-9 y los Esquemas 1, 2 y 4-9. Los datos de ^{1}H NMR y espectroscopias son consistentes con las estructuras de los compuestos.

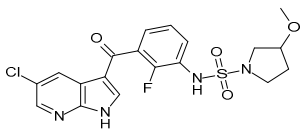
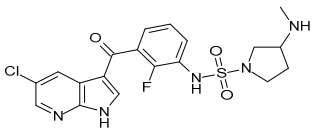
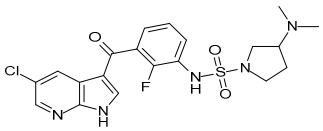
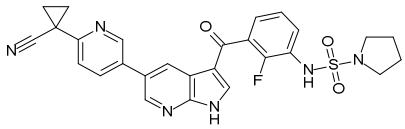
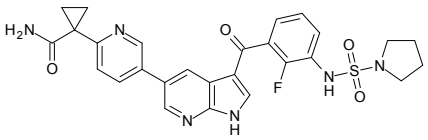
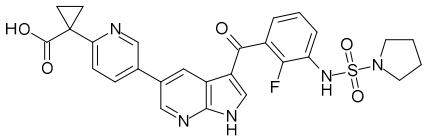
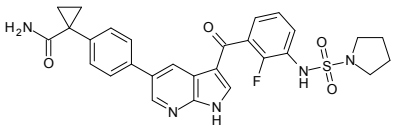
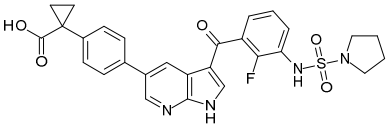
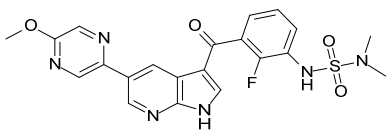
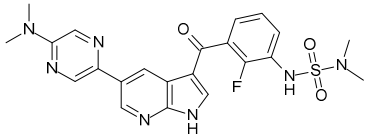
Tabla 3

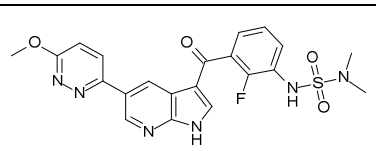
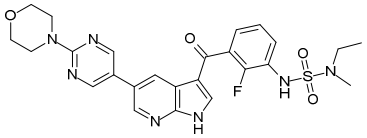
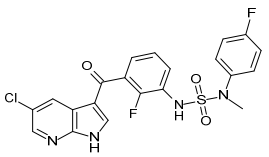
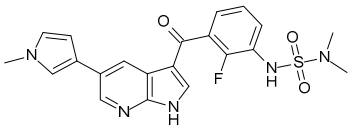
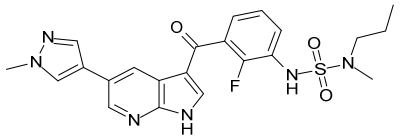
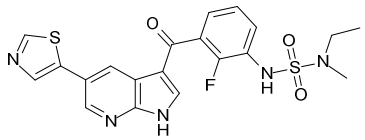
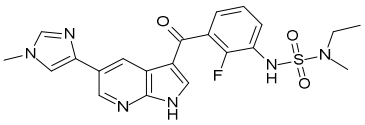
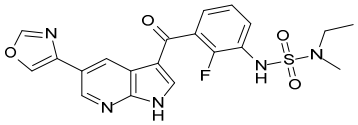
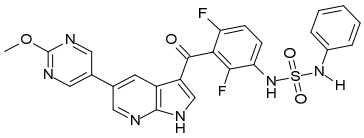
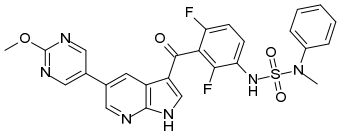
Compuest	Nombre	Estructura
P-0118	[2-fluoro-3-(fenilosulfamoilamino)fenil]-[5-(2	
P-0119	3-[2-fluoro-3-[[metil(fenil)sulfamoil]amino]	
P-0120	[2-fluoro-3-(3-piridilosulfamoilamino)fenil]-[5-(2-	

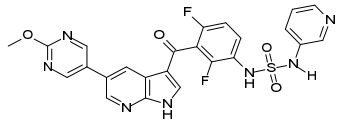
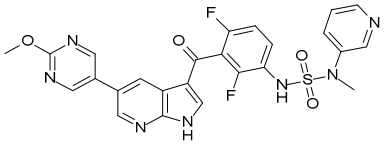
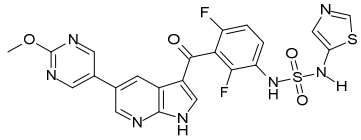
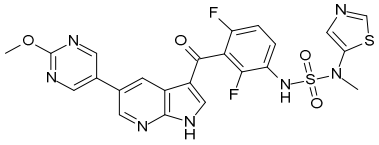
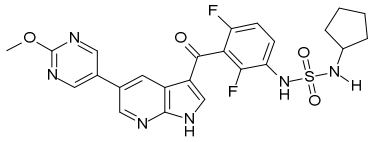
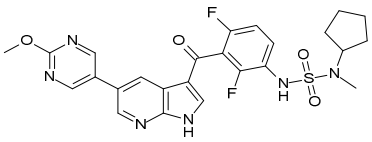
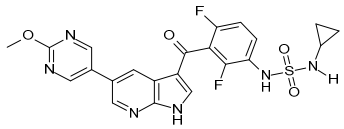
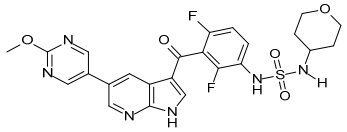
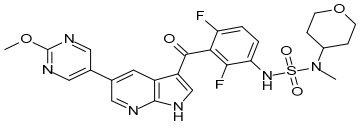
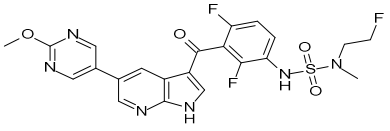
P-0121	3-[2-fluoro-3-[[metil(3-piridi-lo)sulfamoil]amino]benzoil]	
P-0122	[2-fluoro-3-(tiazol-5-ilsulfamoilamino)fenilo]-	
P-0123	5-[[2-fluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-	
P-0124	[3-(ciclopentilosulfamoilami-	
P-0125	3-[3-[[ciclopentilo (me-til)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-	
P-0126	[3-(ciclopropilosulfamoilami-	
P-0127	[2-fluoro-3-(tetrahidropirano-4-ilsulfamoilamino)fenilo]-	
P-0128	3-[2-fluoro-3-[[metil(tetrahidropirano-4-il)sulfamoil]amino]benzoil]	
P-0129	3-[2-fluoro-3-[[2-fluoroe-	
P-0130	3-[2-fluoro-3-[[metil(2,2,2-trifluoroe-	

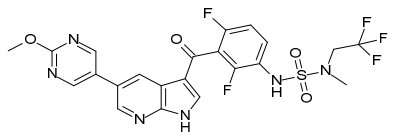
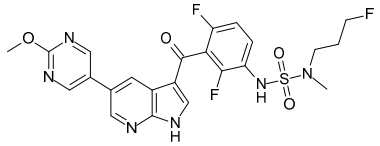
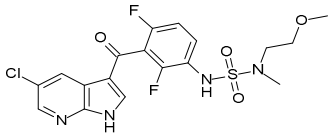
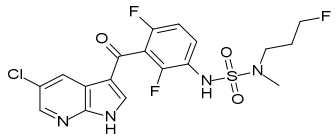
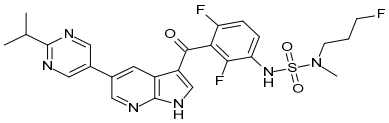
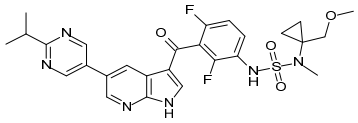
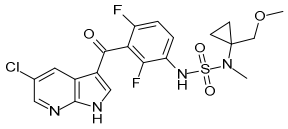
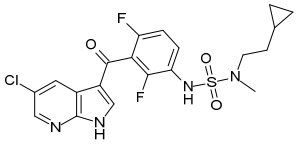
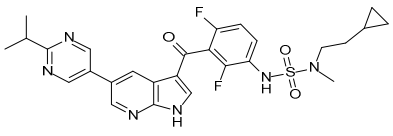
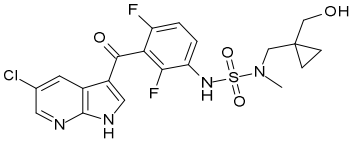
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P-0132	5-cloro-3-[2-fluoro-3-[[2-metoxie-	
P-0133	5-cloro-3-[2-fluoro-3-[[3-fluoropro-	
P-0134	3-[2-fluoro-3-[[3-fluoropro-pil(metil)sulfamoil]amino]b	
P-0135	3-[2-fluoro-3-[[[1-(metoximetil)ciclopropilo]-metil-	
P-0136	5-cloro-3-[2-fluoro-3-[[[1-(metoximetil)ciclopropilo]-metil-	
P-0137	5-cloro-3-[3-[[2-ciclopropiloe-til(metil)sulfamoil]amino]-	
P-0138	3-[3-[[2-ciclopropiloe-til(metil)sulfamoil]amino]-	
P-0139	5-cloro-3-[2-fluoro-3-[[[1-(hidroxime-til)ciclopropilolmetil-	
P-0140	metil 1-[[[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-	

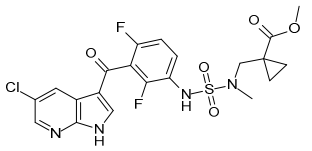
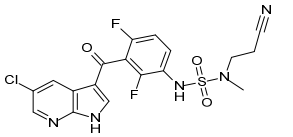
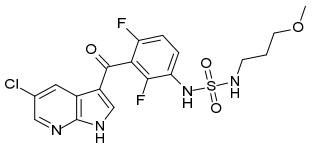
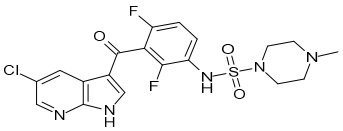
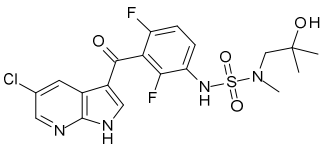
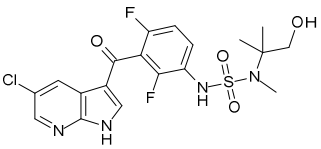
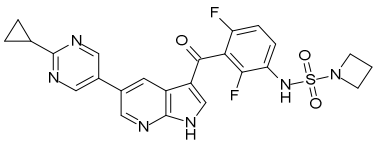
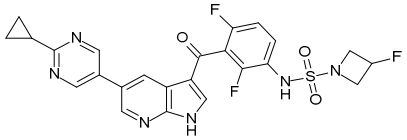
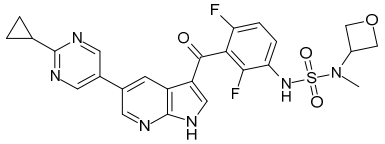
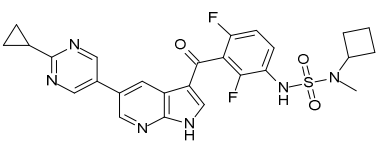
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P-0142	(5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-[2-fluoro-3-(3-	
P-0143	N-[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonil)-2-fluoro-	
P-0144	5-cloro-3-[2-fluoro-3-[[(2-hidroxi-2-metil-propil)-metil-	
P-0145	5-cloro-3-[2-fluoro-3-[[(2-hidroxi-1,1-dimetil-etil)-metil-	
P-0146	N-[3-[5-(2-ciclopropilopirimidin-5-	
P-0147	N-[3-[5-(2-ciclopropilopirimidin-5-	
P-0148	5-(2-ciclopropilopirimidin-5-il)-3-[2-fluoro-3-[[metil(oxetan-3-	
P-0149	3-[3-[[ciclobutilo (metil)sulfamoil]amino]-2-fluoro-benzoil]-5-(2-	
P-0150	5-cloro-3-[2-fluoro-3-[[metil(tetrahidrofuran-3-il)sulfamoil]amino]benzoil]	

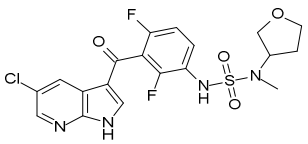
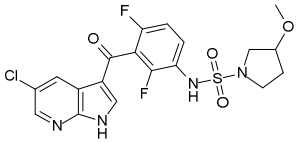
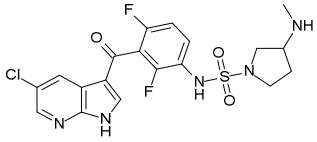
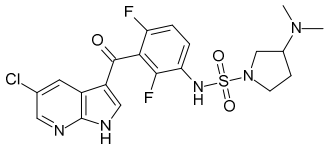
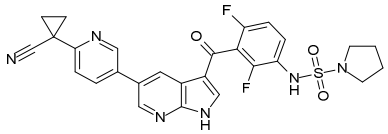
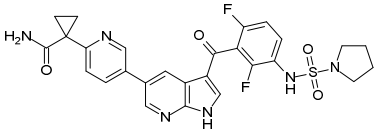
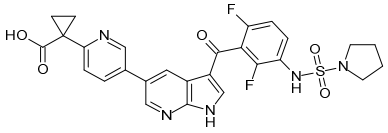
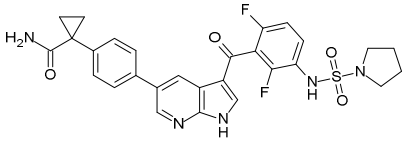
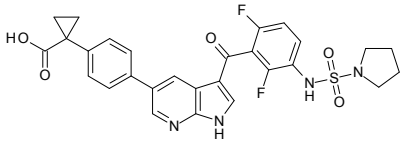
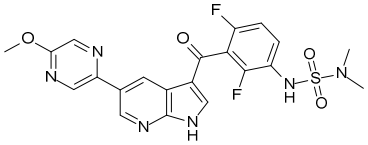
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P-0152	N-[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-	
P-0153	N-[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2-fluoro-	
P-0154	N-[3-[5-[6-(1-cianociclopropilo)-3-piridilo]-1H-pirrolo[2,3-	
P-0155	1-[5-[3-[2-fluoro-3-(pirrolidin-1-ilsulfonilamino)benzoil]-	
P-0156	ácido 1-[5-[3-[2-fluoro-3-(pirrolidin-1-ilsulfonilamino)benzoil]-	
P-0157	1-[4-[3-[2-fluoro-3-(pirrolidin-1-ilsulfonilamino)benzoil]-	
P-0158	ácido 1-[4-[3-[2-fluoro-3-(pirrolidin-1-ilsulfonilamino)benzoil]-	
P-0159	3-[3-(dimetilsulfamoilamino)-2-	
P-0160	5-[5-(dimetilamino)piracin-2-il]-3-[3-(dimetilsulfamoilamino)-2-	

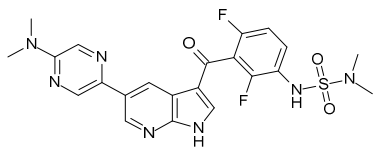
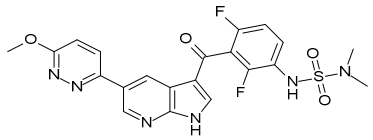
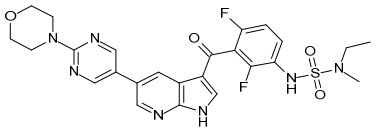
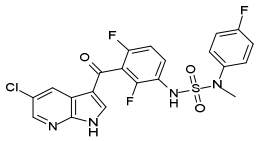
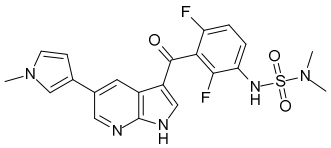
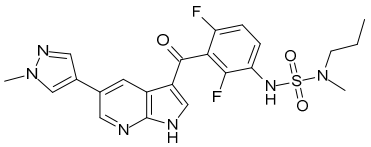
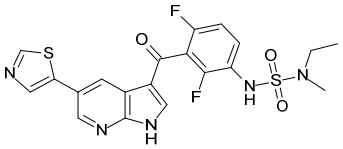
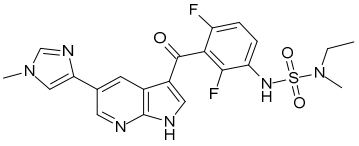
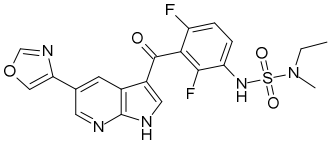
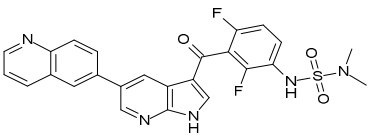
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P-0162	4-[5-[3-[3- [[etil(metil)sulfamoil]amin ol-2-fluoro-benzoil-1H-	
P-0163	5-cloro-3-[2-fluoro-3-[[(4- fluorofenilo)-metil- sulfamoil]amino]benzoil-	
P-0164	3-[3- [[etil(metil)sulfamoil]amin ol-2-fluoro-benzoil-5-(1-	
P-0165	3-[2-fluoro-3- [[me- til(propil)sulfamoil]amino]	
P-0166	5-[3-[3- [[etil(metil)sulfamoil]amin ol-2-fluoro-benzoil-1H-	
P-0167	3-[3- [[etil(metil)sulfamoil]amin ol-2-fluoro-benzoil-5-(1-	
P-0168	4-[3-[3- [[etil(metil)sulfamoil]amin ol-2-fluoro-benzoil-1H-	
P-0169	[2,6-difluoro-3- (fenilosulfamoilami- no)fenilo]-[5-(2-	
P-0170	3-[2,6-difluoro-3- [[me- til(fenilo)sulfamoil]amino]	

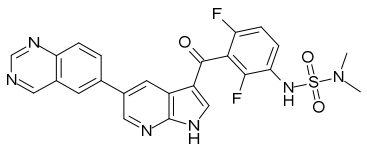
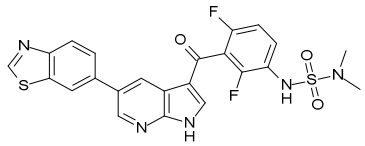
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P-0172	3-[2,6-difluoro-3-[[metil(3-piridi-	
P-0173	[2,6-difluoro-3-(tiazol-5-ilsulfamoilamino)fenilo]-[5-(2-metoxipirimidin-5-	
P-0174	5-[[2,4-difluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-	
P-0175	[3-(ciclopentilosulfamoilamino)-2,6-difluoro-fenilo]-	
P-0176	3-[3-[[ciclopentilo (metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(2-	
P-0177	[3-(ciclopropilosulfamoilamino)-2,6-difluoro-fenilo]-	
P-0178	[2,6-difluoro-3-(tetrahidropirano-4-ilsulfamoilamino)fenilo]-	
P-0179	3-[2,6-difluoro-3-[[metil(tetrahidropirano-4-il)sulfamoil]amino]benzoil]	
P-0180	3-[2,6-difluoro-3-[[2-fluoroe-til(metil)sulfamoil]amino]b	

P-0181	3-[2,6-difluoro-3-[[metil(2,2,2-trifluoroe-	
P-0182	3-[2,6-difluoro-3-[[3-fluoropro-pil(metil)sulfamoillaminolb	
P-0183	5-cloro-3-[2,6-difluoro-3-[[2-metoxie-	
P-0184	5-cloro-3-[2,6-difluoro-3-[[3-fluoropro-	
P-0185	3-[2,6-difluoro-3-[[3-fluoropropil(metil)sulfamoillaminolbenzoill-5-(2-	
P-0186	3-[2,6-difluoro-3-[[[1-(metoximetil)ciclopropilo]-metil-	
P-0187	5-cloro-3-[2,6-difluoro-3-[[[1-(metoximetil)ciclopropilo]-	
P-0188	5-cloro-3-[3-[[2-ciclopropiloe-til(metil)sulfamoillaminol-	
P-0189	3-[3-[[2-ciclopropiloe-til(metil)sulfamoillaminol-	
P-0190	5-cloro-3-[2,6-difluoro-3-[[[1-(hidroxime-	

P-0191	metil 1-[[[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-	
P-0192	5-cloro-3-[3-[[2-cianoe-til(metil)sulfamoil]amino]-	
P-0193	(5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-[2,6-difluoro-3-(3-	
P-0194	N-[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-	
P-0195	5-cloro-3-[2,6-difluoro-3-[[(2-hidroxi-2-metil-propil)-metil-	
P-0196	5-cloro-3-[2,6-difluoro-3-[[(2-hidroxi-1,1-dimetil-etil)-metil-	
P-0197	N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-	
P-0198	N-[3-[5-(2-ciclopropilopirimidin-5-il)-1H-pirrolo[2,3-	
P-0199	5-(2-ciclopropilopirimidin-5-il)-3-[2,6-difluoro-3-[[metil(oxetan-3-	
P-0200	3-[3-[[ciclobutilo (metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-(2-	

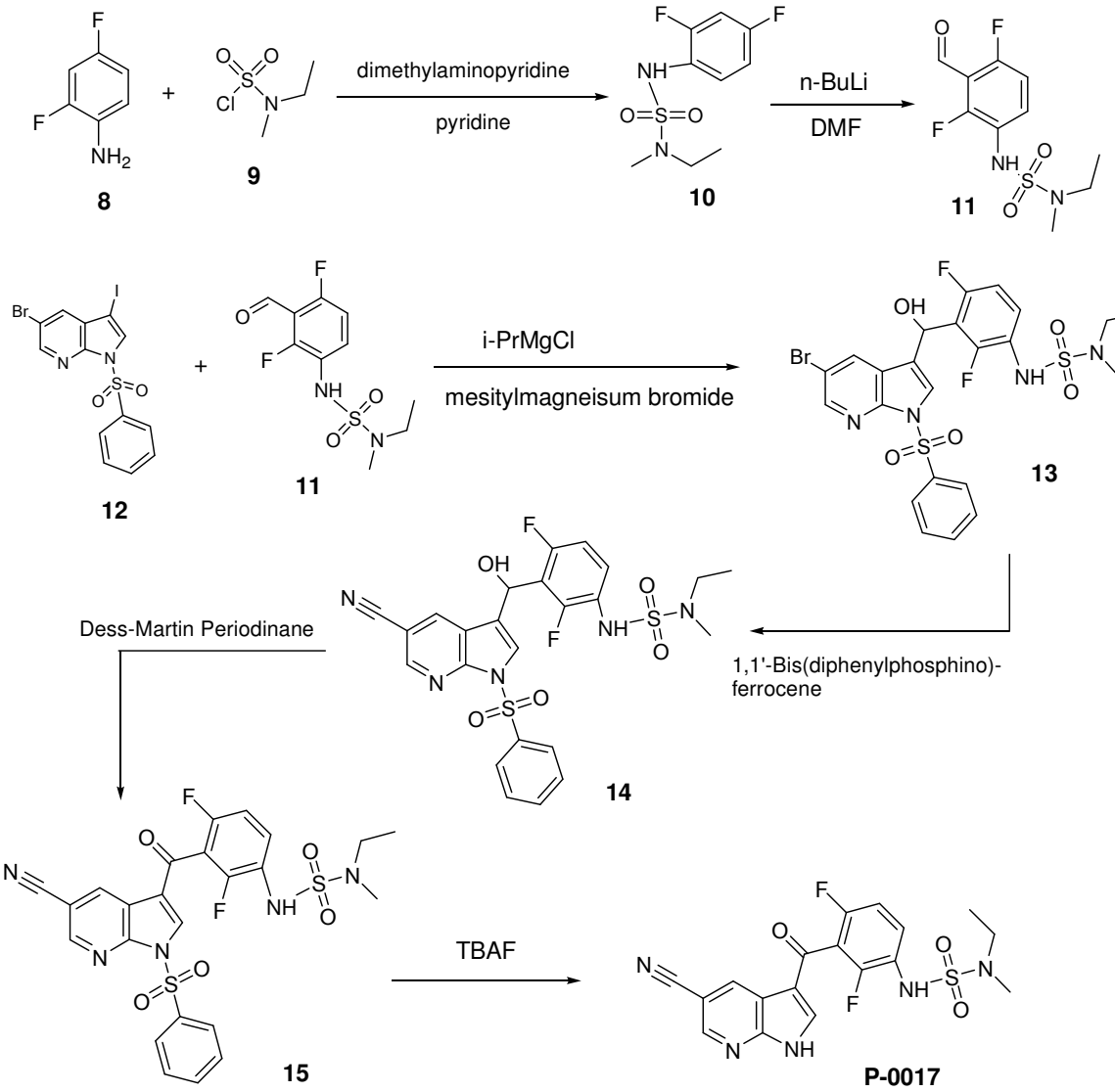
P-0201	5-cloro-3-[2,6-difluoro-3-[[metil(tetrahidrofuran-3-il)sulfamoil]amino]benzoil]-	
P-0202	N-[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-	
P-0203	N-[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-	
P-0204	N-[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-	
P-0205	N-[3-[5-[6-(1-cianociclopropilo)-3-piridilo]-1H-pirrolo[2,3-	
P-0206	1-[5-[3-[2,6-difluoro-3-(pirrolidin-1-ilsulfonilamino)benzoil]-	
P-0207	Ácido 1-[5-[3-[2,6-difluoro-3-(pirrolidin-1-ilsulfonilamino)benzoil]-	
P-0208	1-[4-[3-[2,6-difluoro-3-(pirrolidin-1-ilsulfonilamino)benzoil]-	
P-0209	Ácido 1-[4-[3-[2,6-difluoro-3-(pirrolidin-1-ilsulfonilamino)benzoil]-	
P-0210	3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-5-(5-	

P-0211	5-[5-(dimetilamino)piracin-2-il]-3-[3-(dimetilsulfamoilamino)-	
P-0212	3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-5-(6-	
P-0213	4-[5-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-	
P-0214	5-cloro-3-[2,6-difluoro-3-[[(4-fluorofenilo)-metil-sulfamoil]amino]benzoil]-	
P-0215	3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-5-(1-	
P-0216	3-[2,6-difluoro-3-[[metil(propil)sulfamoil]amino]	
P-0217	5-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-	
P-0218	3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-5-	
P-0219	4-[3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-	
P-0220	6-[3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-1H-	

P-0221	6-[3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-1H-	
P-0222	6-[3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-1H-	

Ejemplo 3: Preparación de 5-ciano-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina (P-0017).

Esquema 3



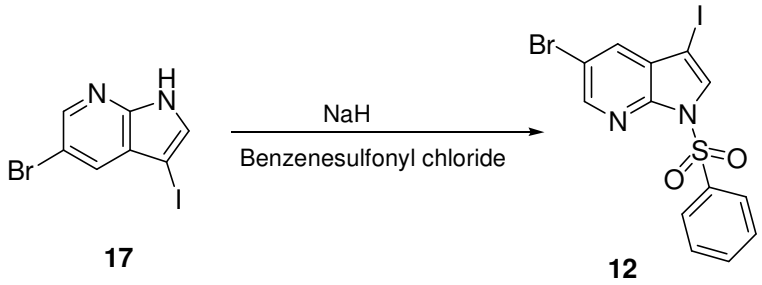
[0207] Síntesis de 1-[(etil(metil)sulfamoil)amino]-2,4-difluoro-benceno (10): A una solución de 2,4-Difluoroanilina (2,21 g, 17,13 mmol) en dicloroetano (10 mL) se agregó 4-Dimetilaminopiridina (0,1 g, 0,82 mmol), N-etil-N-metil-sulfamoil cloruro (2,7 g, 17,13 mmol) y piridina (2 g, 25,28 mmol). Se agitó la mezcla a temperatura ambiente de un día para otro. Se vertió la mezcla obtenida en una solución acuosa de carbonato de potasio y se extrajo con etil acetato (EtOAc). La capa orgánica fue lavada con salmuera, se secó con sulfato de

sodio y filtrado. Se concentró y purificó el filtrado mediante cromatografía de columna con gel de sílice usando 20% a 100% etil acetato en hexano como eluyente para obtener el producto deseado (**10**, 3,08 g, 71,8% rendimiento). MS (ESI) $[M+H^+]^+$ = 250,8. El espectro ^1H NMR es consistente con la estructura del compuesto.

[0208] Síntesis de 1-[(etil(metil)sulfamoil)amino]-2,4-difluoro-3-formilo-benceno (11): A una mezcla de 1-[(etil(metil)sulfamoil)amino]-2,4-difluoro-benceno (**10**, 3,08 g, 12,31 mmol) en tetrahidrofuran (THF) (25,0 mL) a una atmósfera de nitrógeno a -78 °C se agregó 2,5M n-butillitio (n-BuLi) en THF (5 mL). Se mantuvo la mezcla de reacción incolora a -78 °C durante una hora y se agregó 2,5M n-BuLi en THF (5,4 ml) a la mezcla de reacción. Se mantuvo la reacción a -78 °C durante 1 hr y se agregó N,N-Dimetilformamida (DMF) (1,8 mL, 23,25 mmol). La mezcla de reacción se convirtió en un sólido. Se agitó la mezcla de reacción sólida durante aproximadamente 5 minutos para obtener un compuesto acuoso. Se mantuvo la mezcla de reacción en un baño de acetona glacial durante 1 hr y se dejó calentar hasta temperatura ambiente durante 1 hora. Se vertió la mezcla de reacción en una solución acuosa de cloruro de amoniaco y se extrajo con etil acetato. La capa orgánica fue lavada con salmuera, se secó con sulfato de sodio, se concentró y purificó con cromatografía de columna de gel de sílice usando 30% a 100% etil acetato en hexano como eluyente para obtener el producto deseado

(**11**, 1,10 g, 32,1% rendimiento). MS (ESI) $[M+H^+]^+$ = 278,8. El espectro ^1H NMR es consistente con la estructura del compuesto.

[0209] Síntesis de 1-(bencenosulfonil)-5-bromo-3-yodo-pirrolo[2,3-b]piridina (12).



17 **12**

[0210] A una solución de 5-bromo-3-yodo-1H-pirrolo[2,3-b]piridina (2,7 g, 8,36 mmol) en DMF (30,0 mL) se agregó hidruro de sodio (60%, 0,37 g, 9,2 mmol) a temperatura ambiente. Al cabo de 10 minutos, se agregó cloruro de bencenosulfonilo (1,13 ml, 8,78 mmol) y se agitó la mezcla de reacción a temperatura ambiente durante 3 horas. Se vertió la mezcla de reacción en agua y se extrajo con etil acetato. La capa orgánica se secó con sulfato de sodio anhidroso y filtrado. Se concentró el filtrado, se filtró y lavó con etil acetato para obtener el producto deseado **12** en forma de sólido blanco (2,70 g). Se purificó el líquido madre mediante cromatografía de columna de gel de sílice usando 20% a 100% etil acetato en hexano como eluyente para obtener el producto de adición (0,90 g). El rendimiento combinado es de 93,0%. MS (ESI) $[M+H^+]^+$ = 464,1. El espectro ^1H NMR es consistente con la estructura del compuesto.

[0211] Síntesis de 1-(bencenosulfonil)-5-bromo-3-[[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-fenilo]-hidroxi-metil]pirrolo[2,3-b]piridina (13):

Paso 1: A una solución de 1-[[etil(metil)sulfamoil]amino]-2,4-difluoro-3-formilo-benceno (**11**, 0,76 g, 2,73 mmol) en THF (5 mL), en nitrógeno a -78 °C, se agregó 1M bromuro de mesitilmagnesio en THF (2,8 ml). Se agitó la solución de la reacción durante 40 minutos.

Paso 2: A 1-(bencenosulfonil)-5-bromo-3-yodo-pirrolo[2,3-b]piridina (**17**, 1,76 g, 3,79 mmol) en THF (10 mL), a una atmósfera de nitrógeno a -40 °C, se agregó una solución de i-PrMgCl (2,0 M en THF, 1,9 mL). Se dejó que la mezcla de reacción se calentara hasta 5 °C en 1 hora. Se enfrió la mezcla de reacción hasta -40 °C y se agregó la solución de reacción del paso 1. Se dejó que la mezcla de reacción obtenida se calentara hasta temperatura ambiente en 1 hr, se vertió en agua y se extrajo con etil acetato. La capa orgánica fue lavada con salmuera, se secó con sulfato de sodio, se concentró y purificó mediante cromatografía de columna con gel de sílice usando 20% a 100% etil acetato en hexano como eluyente para obtener el producto deseado (**13**, 1,10g, 65,4%). MS (ESI) $[M+H^+]^+$ = 614,7 y 616,7. El espectro ^1H NMR es consistente con la estructura del compuesto.

[0212] Síntesis de 1-(bencenosulfonil)-5-ciano-3-[[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-fenilo]-hidroxi-metil]pirrolo[2,3-b]piridina (14): A 1-(bencenosulfonil)-5-

bromo-3-[[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-fenilo]-hidroxi-metil]pirrolo[2,3-b]piridina (**13**, 500 mg, 0,81 mmol) se agregó cianuro de zinc (0,05 ml, 0,77 mmol), zinc, tris(dibenciloideneacetona)dipaladio (0) (90 mg, 0,09 mmol), 1,1'-Bis(difenilofosfino)ferroceno (90 mg, 0,16 mmol) y DMF (10 ml) en nitrógeno. Se calentó la mezcla de reacción a 120 °C de un día para otro. Se vertió la mezcla de reacción obtenida en una solución acuosa de carbonato de potasio y se extrajo con etil acetato. La capa orgánica fue lavada con salmuera, se secó con sulfato de sodio y se filtró. Se concentró y purificó el filtrado mediante cromatografía de columna de gel de sílice usando 20% a 100% etil acetato en hexano como eluyente para obtener el producto deseado (**14**, 0,20 g, 43,8% rendimiento). MS (ESI) $[M+H^+]^+$ = 562,0. El espectro ^1H NMR es consistente con la estructura del compuesto.

[0213] Síntesis de 1-(bencenosulfonil)-5-ciano-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]pirrolo[2,3-b]piridina (15): A 1-(bencenosulfonil)-5-ciano-3-[[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-fenilo]-hidroxi-metil]pirrolo[2,3-b]piridina (**14**, 0,2 g, 0,36 mmol) en cloruro de metileno (10 mL) se agregó Periodinano Dess-Martin (0,18 g, 0,43 mmol). La mezcla de reacción fue agitada a temperatura ambiente durante 20 minutos. Se concentró la mezcla de reacción y se purificó mediante cromatografía de columna con gel de sílice usando 25% a 100% etil acetato en hexano como eluyente para ob-

tener el producto deseado (**15**, 170 mg, 85,3% rendimiento). MS (ESI) $[M+H^+]^+$ = 560,5. El espectro ^1H NMR es consistente con la estructura del compuesto.

[0214] Síntesis de 5-ciano-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina (P-0017): A 1-(bencenosulfonil)-5-ciano-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]pirrolo[2,3-b]piridina (**15**, 0,17 g, 0,3 mmol) en THF (10 mL) se agregó tetra-n-butilamonio fluoruro (TBAF) (0,19 g, 0,61 mmol). La mezcla de reacción fue agitada a temperatura ambiente de un día para otro. Se vertió la mezcla de reacción obtenida en una solución acuosa de cloruro de amoniaco y se extrajo con etil acetato. La capa orgánica fue lavada con salmuera, se secó con sulfato de sodio y filtrado. Se concentró y purificó el filtrado mediante cromatografía de columna con gel de sílice usando 2% a 10% metanol en cloruro de metileno como eluyente para obtener el producto (**P-0017**, 74,5 mg, 58,5% rendimiento). MS (ESI) $[M+H^+]^+$ = 420,1. El espectro ^1H NMR es consistente con la estructura del compuesto.

[0215] Se prepararon los compuestos siguientes de conformidad con los protocolos establecidos en el Ejemplo 3 y Esquema 3.

5-cloro-3-[3-[[etil(metil)sulfamoil]amino]-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0012)**,

N-[2,4-difluoro-3-(5-fluoro-4-yodo-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]pirrolodina-1-sulfonamida **(P-0013)**,

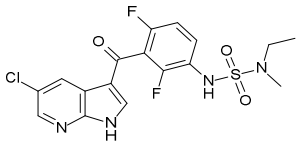
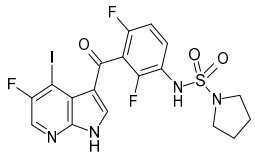
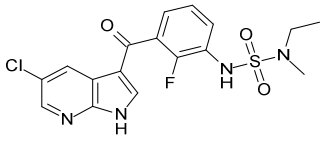
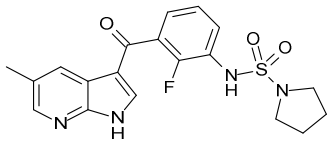
5-cloro-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0018),**

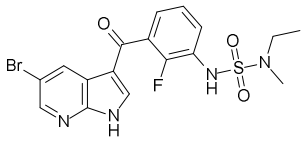
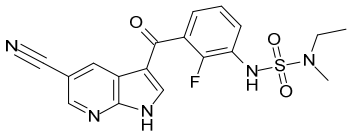
N-[2-fluoro-3-(5-metil-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]pirrolodina-1-sulfonamida **(P-0023),**

5-bromo-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0038),**

5-ciano-3-[3-[[etil(metil)sulfamoil]amino]-2-fluoro-benzoil]-1H-pirrolo[2,3-b]piridina **(P-0039).**

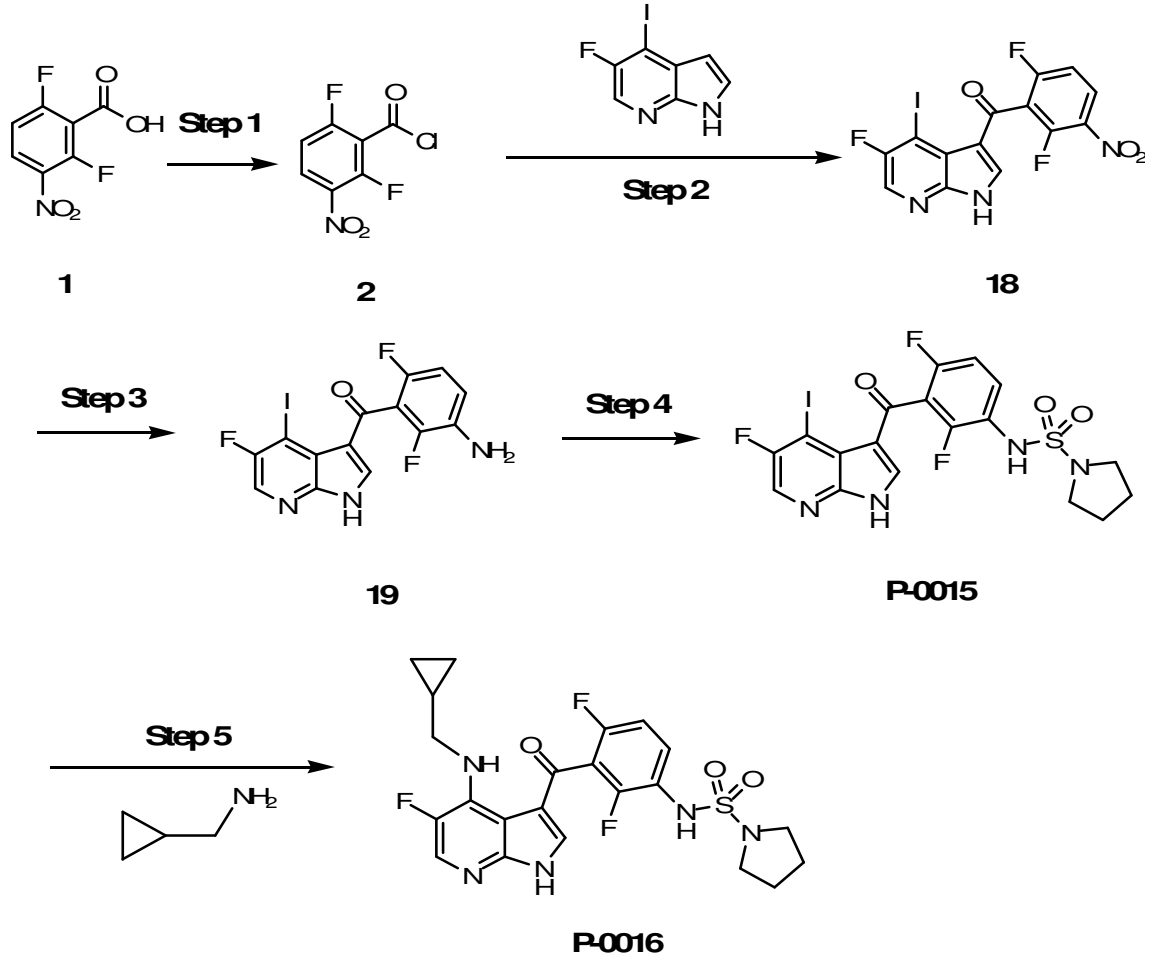
La tabla siguiente proporciona estructuras de ciertos compuestos de la presente invención y masa observada. El espectro ^{1}H NMR fue consistente con las estructuras de los compuestos.

	Compuestos	MS(ESI) $[M+H^+]^+$ observada
P-0012		428,9
P-0015		551,1
P-0018		410,9
P-0023		402,9

P-0038		455,0
P-0039		454,9 y 456,9

Ejemplo 4: Preparación de N-[3-[4-(ciclopropilometiloamino)-5-fluoro-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo]pirrolodina-1-sulfonamida (P-0016).

Esquema 4.



[0216] Paso 1 - Síntesis de 2,6-difluoro-3-nitrocloruro de

benzoilo (2): En un matraz redondo, se agregó ácido 2,6-difluoro-3-nitrobenzoico (5,5 g, 0,03 mol) cloruro de tionilo (20 mL, 0,27 mol) y N,N-Dimetilformamida (100 µl, 0,001 mol). Se colocó la mezcla de reacción en un baño de aceite a 80 °C durante 4 hrs. Se retiraron todos los volátiles y se depuró el residuo de tolueno dos veces y se secó en alto vacío para producir un líquido aceitoso amarillo (**2**, 5,95 g, 99%). Se usará sin modificaciones.

[0217] Paso 2 - Síntesis de (2,6-difluoro-3-nitro-fenilo)-(5-fluoro-4-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona (18): En un vial, se enfrió 5-fluoro-4-yodo-1H-pirrolo[2,3-b]piridina (450 mg, 1,72 mmol) en un baño de agua glacial y se agregó ácido trifluorometanosulfónico (1,52 ml, 17,17 mmol). Se agitó la reacción en un baño de agua glacial durante 5 minutos y seguidamente se agregó 2,6-difluoro-3-nitrocloruro de benzoilo (**2**, 500mg, 2,26 mmol). La mezcla de reacción obtenida fue agitada en un baño de agua glacial durante 20 min y se calentó hasta temperatura ambiente. Después de 24 hrs a temperatura ambiente, se mitigó la mezcla de reacción con 5 mL de metanol y se agitó a r.t. durante 1 hr. Se vertió la mezcla en solución acuosa saturada de $NaHCO_3$ y se extrajo con EtOAc. Se lavó la capa orgánica con agua y salmuera, se secó con $MgSO_4$. Se retiraron los volátiles en vacío. Se suspendió el residuo en acetonitrilo y se sonicó durante 45 mins. Se recogió el material precipitado mediante filtración y se lavó con acetonitrilo. El producto deseado

(**18**, 532 mg, 69%) fue un sólido de color tostado. MS (ESI) $[M+H^+]^+$ = 447,8.

[0218] Paso 3 – Preparación de (3-amino-2,6-difluoro-fenilo)-(5-fluoro-4-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona (19): En un matraz redondo, se agregó a (2,6-difluoro-3-nitro-fenilo)-(5-fluoro-4-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona (0,53 g, 0,001 mol) EtOH (50 ml) y TIN(II) cloruro (788 mg, 4,16 mmol). Se calentó la mezcla de reacción a 50 °C durante el fin de semana. La mezcla de reacción fue tratada con 50 mL de agua y 50 mL de bicarbonato de sodio saturado. Se agregó etil acetato adicional (20 mL) y se trató la suspensión lechosa con celita y se mezcló bien antes del filtrado. Se agregó el filtrado mediante salmuera para producir capas transparentes que fueron separadas. Se lavó la capa orgánica con agua y salmuera y se secó con MgSO4. Se retiraron los volátiles en vacío. El producto deseado fue aislado mediante cromatografía de columna con gel de sílice (EtOAc/Hexano, gradiente 0–80%) como un sólido blanquecino (**19**, 365 mg, 73%). MS (ESI) $[M+H^+]^+$ = 417,9.

[0219] Paso 4 – Preparación de N-[2,4-difluoro-3-(5-fluoro-4-yodo-1H-pirrolo[2,3-b]piridina-3-carbonilo)fenilo]pirrolodina-1-sulfonamida (P-0015): En un matraz redondo, se disolvió (3-amino-2,6-difluoro-fenilo)-(5-fluoro-4-yodo-1H-pirrolo[2,3-b]piridin-3-il)metanona (**19**, 180 mg, 0,43 mmol) en 4 mL de THF y se agregó piridina (106 µl, 1,29 mmol) y pirrolodina-1-sulfonilo cloruro (110 mg, 0,65 mmol). La solución fue agitada a tempera-

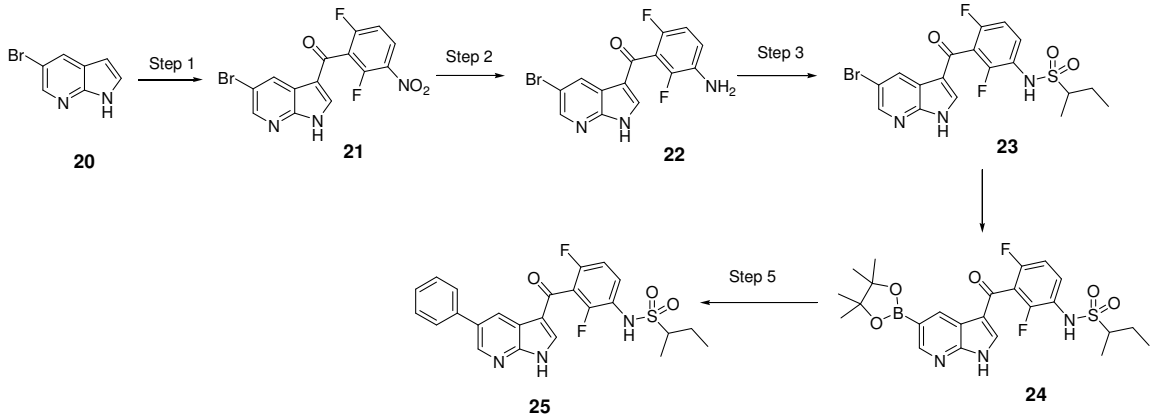
tura ambiente durante aproximadamente 90 hrs. La mezcla de reacción se agregó agua y se extrajo con etil acetato. Se lavó la capa orgánica con agua y salmuera y se secó mediante MgSO4. Se retiraron los volátiles en vacío. El producto deseado fue aislado mediante cromatografía de columna con gel de sílice (EtOAc/Hexano, 0–80% gradiente) en forma de sólido amarillo claro (**P–0015**, 99 mg, 41%). MS (ESI) $[M+H^+]^+$ = 551,1.

[0220] Paso 5 – Preparación de N–[3–[4–(ciclopropilometiloamino)–5–fluoro–1H–pirrolo[2,3–b]piridina–3–carbonilo]–2,4–difluoro–fenilo]pirrolodina–1–sulfonamida (P–0016): A N–[2,4–difluoro–3–(5–fluoro–4–yodo–1H–pirrolo[2,3–b]piridina–3–carbonilo)fenilo]pirrolodina–1–sulfonamida (95mg, 0,17 mmol) en alcohol isopropílico (2 ml) se agregó ciclopropilomethanamina (0,5 mL, 49,11mg, 0,69 mmol). Se agitó la solución obtenida a 90 °C de un día para otro. La mezcla de reacción fue concentrada in vacuo y se purificó mediante gel de sílice en compañía de un cartucho de 8 g usando EtOAc/Hexano (0– gradiente 65%) como eluyente. Se purificó adicionalmente el producto obtenido mediante HPLC preparatoria. Se combinaron las fracciones puras y se secaron en un liofilizador. Se obtuvo el producto deseado en forma de un sólido color tostado (**P–0016**, 6,5 mg, 7,6% rendimiento). MS (ESI) $[M+H^+]^+$ = 494,4. El espectro H^1 NMR(THF–d_8) es consistente con la estructura del compuesto.

Ejemplo 5: Síntesis de N-(2-Cloro-5-{3-[2,6-difluoro-3-(propano-1-sulfonilamino)-benzoil]-1H-pirrolo[2,3-b]piridin-5-il}-piridin-3-il)-bencenosulfonamida 25

[0221] Se preparó N-(2-Cloro-5-{3-[2,6-difluoro-3-(propano-1-sulfonilamino)-benzoil]-1H-pirrolo[2,3-b]piridin-5-il}-piridin-3-il)-bencenosulfonamida **7** en seis pasos de 5-Bromo-1H-pirrolo[2,3-b]piridina **1** según se muestra en el Esquema 1.

Esquema 5



*Paso 1 – Preparación de 2,6-Difluoro-3-nitro-fenilo)-(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)-metanona (**21**):*

[0222] A 5-Bromo-1H-pirrolo[2,3-b]piridina (**20**, 0,5 g, 2 mmol) en nitrometano (11 mL) se agregó aluminio tricloruro (1,64 g, 12 mmol). La mezcla se volvió transparente de manera instantánea. La solución obtenida fue agitada a temperatura ambiente durante 1 hora. A esta mezcla se agregó seguidamente 2,6-difluoro-3-nitro-cloruro de benzoilo (0,681 g, 3 mmol) en nitrometano. La mezcla de reacción fue agitada a 45 °C de un día para otro. Se mitigó la reacción con metanol. Después de algunos minutos, salieron algunos sólidos por colisión. Se recogieron los

sólidos mediante filtración y se observó un producto limpio (**21**, 0,58 g). Se obtuvo un producto adicional del filtrado a través de cromatografía (eluido con etil acetato y diclorometano).

[0223] Preparación de 2,6-Difluoro-3-nitro-benzoil cloruro: A un ácido 2,6-Difluoro-3-nitro-benzoico (2 g, 1 mmol) se agregó cloruro de tionilo (0,9 mL, 12 mmol). La mezcla de reacción fue agitada a 57 °C de un día para otro. Después de retirar el solvente, se depuró el residuo una vez del tolueno. Lo anterior produjo un aceite marrón el cual fue sometido a NMR con el resultado de una conversión completa al cloruro del ácido (18 g, 99%). Este material se usó sin cambios y sin purificación.

*Paso 2 - Preparación de (3-Amino-2,6-difluoro-fenilo)-(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)-metanona (**22**):*

[0224] A una suspensión de 2,6-difluoro-3-nitro-fenilo)-(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)-metanona (0,123 g, 0,287 mmol) en etil acetato (5 mL) y tetrahidrofurano (5 mL) se agregó cloruro de estaño, dihidrato (0,223 g, 1 mmol). La mezcla de reacción fue agitada a 60 °C durante 24 horas. La mezcla de reacción fue vertida en una mezcla de 25 mL de agua y 25 mL de bicarbonato de sodio saturado. Esta mezcla lechosa fue filtrada a través de un lecho de celita y el lecho de celita fue lavado con una porción de etil acetato. Se separaron las dos capas del filtrado. Se recogió la capa orgánica, se lavó con salmuera y se secó con sulfato de sodio anhidroso. Después de retirar el agente de secado y el solvente, se purificó el residuo mediante cro-

matografía (eluido con etil acetato y diclorometano) para proporcionar el producto sólido (**22**, 0,1 g, 87%).

*Paso 3 – Preparación de ácido isobutano-1-sulfónico [3-(5-bromo-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-difluoro-fenilo]-amida (**23**):*

[0225] Se irradió una mezcla de (3-Amino-2,6-difluoro-fenilo)-(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)- metanona (47 mg, 0,13 mmol), isobutano-1-sulfonilcloruro (62 mg, 0,4 mmol) y piridina (0,5 mL, 6 mmol), en tetrahidrofurano (3 mL) en microondas a 130°C durante 10 minutos. Se diluyó la mezcla mediante etil acetato y seguidamente se lavó con agua, salmuera y se secó con sulfato de sodio anhidroso. Después de retirar el agente de secado y el solvente, se purificó el residuo mediante cromatografía (eluido con hexanos y etil acetato) para proporcionar el producto deseado (**23**, 24 mg, 36%).

*Paso 4 – Preparación de ácido isobutano-1-sulfónico {2,4-difluoro-3-[5-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-fenilo}-amida (**24**):*

[0226] A una suspensión de compuesto **23**, una cantidad apropiada de bis(pinacolato)diboro y se agrega acetato de potasio en solvente de 1,4-dioxano anhidroso o un solvente apropiado [1,1'-Bis(difenilofosfino)ferroceno]dicloropaladio (II) (en complejo con diclorometano 1:1). La suspensión se calienta en un baño de aceite durante 2 a 24 horas. Después de enfriar hasta temperatura ambiente se diluye la mezcla con etil acetato, se filtra a

través de una almohadilla de celita y se concentra. Se purifica el residuo mediante cromatografía para proporcionar ácido isobutano-1-sulfónico {2,4-difluoro-3-[5-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]-fenilo}-amida (**24**).

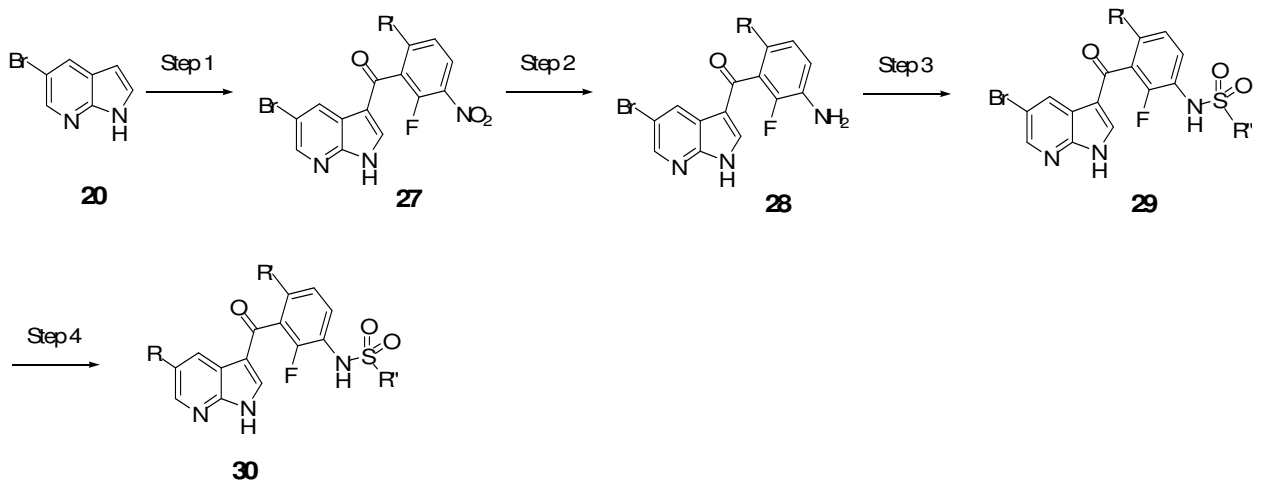
*Paso 5 - Preparación de ácido isobutano-1-sulfónico {3-[5-fenilo-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo}-amida (**25**):*

[0227] A una mezcla de compuesto **24**, fenilo bromuro y una cantidad apropiada de carbonato de cesio en 1,4-dioxano anhidroso o un solvente apropiado se agrega una cantidad apropiada de tetraquis(trifenilofosfina)paladio. Seguidamente se caliente la mezcla en un baño de aceite durante 2 a 48 horas. Después de enfriar hasta temperatura ambiente, se diluye la mezcla con etil acetato o un solvente apropiado, se filtra a través de celita y se concentra. Se purificó el residuo mediante cromatografía para proporcionar ácido isobutano-1-sulfónico {3-[5-fenilo-1H-pirrolo[2,3-b]piridina-3-carbonilo]-2,4-difluoro-fenilo}-amida (**25**).

Ejemplo 6: Preparación del compuesto 30

[0228] El compuesto **30** se prepara en cuatro pasos a partir de 5-Bromo-1H-pirrolo[2,3-b]piridina **1** según se muestra en el Esquema 2.

Esquema 6



*Paso 1 – Preparación del compuesto **27:***

[0229] A 5-Bromo-1H-pirrolo[2,3-b]piridina (**20**) en nitrometano o un solvente apropiado se agrega una cantidad apropiada de aluminio tricloruro. La solución obtenida se agita a temperatura ambiente durante 1 a 24 horas (calentado en un baño de aceite de ser necesario). A esta mezcla se agrega seguidamente una cantidad apropiada de cloruro de benzoilo en nitrometano o un solvente apropiado. La mezcla de reacción se calienta en un baño de aceite durante 2 a 48 horas. Se mitiga la reacción con metanol o un solvente apropiado. Se recoge el precipitado mediante filtración y se purifica mediante cromatografía para proporcionar el compuesto **27.**

*Paso 2 – Preparación del compuesto **28:***

[0230] A una suspensión del compuesto **20** en un solvente apropiado se agrega una cantidad apropiada de cloruro de estaño. La mezcla de reacción se calienta en un baño de aceite durante 2 a 48 horas. La mezcla de reacción se vierte en una mezcla de agua

y bicarbonato de sodio saturado. Esta mezcla lechosa fue filtrada a través de un lecho de celita y el lecho de celita fue lavado con un solvente apropiado. Se recogieron las capas orgánicas, se lavaron con salmuera y se secaron con sulfato de sodio anhidroso. Después de retirar el agente de secado y el solvente, se purifica el residuo mediante cromatografía para proporcionar el compuesto **28**.

*Paso 3 – Preparación del compuesto **29**:*

[0231] Una mezcla de compuesto **28**, un cloruro de sulfonio apropiado y una cantidad apropiada de piridina en un solvente apropiado se irradia en microondas por encima de 50°C durante 10 a 60 minutos. Se diluye la mezcla mediante un solvente apropiado y seguidamente se lava con agua, salmuera y se seca con sulfato de sodio anhidroso. Después de retirar el agente de secado y el solvente, se purifica el residuo mediante cromatografía para proporcionar el compuesto **29**.

*Paso 4 – Preparación del compuesto **30**:*

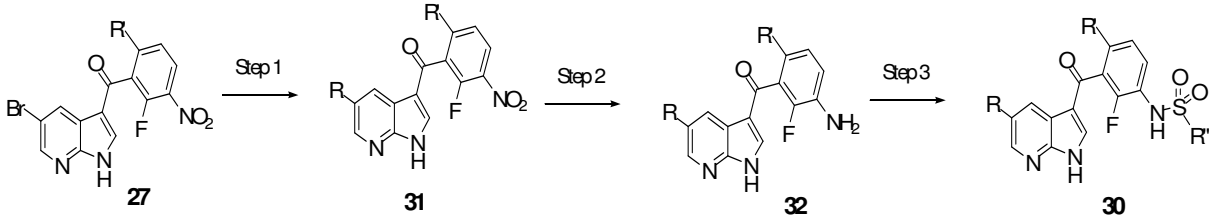
[0232] A una mezcla de compuesto **29**, un ácido borónico o éster borónico apropiado y una cantidad apropiada de carbonato de cesio en 1,4-dioxano anhidroso o un solvente apropiado se agrega una cantidad apropiada de tetraquis(trifenilofosfina)paladio. Seguidamente se calienta la mezcla en un baño de aceite durante 2 a 48 horas. Después de enfriar hasta temperatura ambiente, se diluye la mezcla con etil acetato o un solvente apropiado, se filtra a través de celita y

se concentra. Se purifica el residuo mediante cromatografía para proporcionar el compuesto **30**. Cuando no está disponible comercialmente ácido borónico o éster borónico, se prepara el ácido borónico o éster del compuesto **29** siguiendo el procedimiento descrito en el Ejemplo 1, paso 4. Seguidamente se prepara el compuesto **30** siguiendo el procedimiento anteriormente mencionado del ácido borónico o éster de compuesto **29** y un haluro apropiado.

Ejemplo 7: Preparación del compuesto 30

[0233] También puede prepararse el compuesto **30** en tres pasos a partir de 5-Bromo-1H-pirrolo[2,3-b]piridina **11** según se muestra en el Esquema 3.

Esquema 7



*Paso 1 - Preparación del compuesto **31:***

[0234] A una mezcla de compuesto **27**, un ácido borónico o a éster borónico apropiado y una cantidad apropiada de carbonato de cesio en 1,4-dioxano anhidroso o un solvente apropiado se agrega una cantidad apropiada de tetraquis(trifenilofosfina)paladio. Seguidamente se calienta la mezcla en un baño de aceite durante 2 a 48 horas. Después de en-

friar hasta temperatura ambiente, se diluye la mezcla con etil acetato o un solvente apropiado, se filtró a través de celita y se concentró. Se purificó el residuo mediante cromatografía para proporcionar el compuesto **31**. Cuando no está disponible comercialmente el ácido borónico o un éster borónico, se prepara el ácido borónico o éster del compuesto **27** siguiendo el procedimiento descrito en el Ejemplo 1, paso 4. Seguidamente se prepara el Compuesto **31** siguiendo el procedimiento mencionado anteriormente a partir de ácido borónico o éster del compuesto **27** y un haluro apropiado.

*Paso 2 – Preparación del compuesto **32:***

[0235] A una suspensión del compuesto **31** en un solvente apropiado se agrega una cantidad apropiada de cloruro de estaño. La mezcla de reacción se calienta en un baño de aceite durante 2 a 48 horas. Se vierte la mezcla de reacción en una mezcla de agua y bicarbonato de sodio saturado. Esta mezcla lechosa fue filtrada a través de un lecho de celita y se lavó el lecho de celita con un solvente apropiado. Se recogieron las capas orgánicas, se lavaron con salmuera y se secaron con sulfato de sodio anhidroso. Después de retirar el agente de secado y el solvente, se purificó el residuo mediante cromatografía para proporcionar el compuesto **32.**

*Paso 3 – Preparación del compuesto **30:***

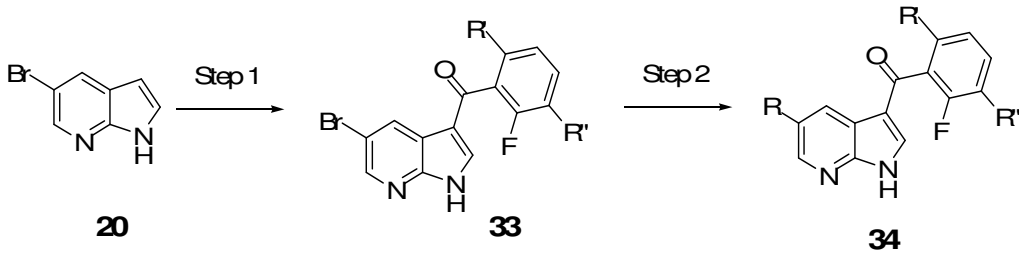
[0236] Una mezcla de compuesto **32**, un cloruro de sulfonio apropiado y una cantidad apropiada de piridina en un solvente

apropiado es irradiada en microondas a más de 50°C durante 10 a 60 minutos. Se diluye la mezcla mediante un solvente apropiado y seguidamente se lava con agua, salmuera y se seca con sulfato de sodio anhidroso. Después de retirar el agente de secado y el solvente, se purifica el residuo mediante cromatografía para proporcionar el compuesto **30.**

Ejemplo 8: Preparación del compuesto 34

[0237] El compuesto **34** se prepara en dos pasos a partir de 5-Bromo-1H-pirrolo[2,3-b]piridina **1** según se muestra en el Esquema 8.

Esquema 8.



20 **33** **34**

*Paso 1 – Preparación del compuesto **33:***

[0238] A 5-Bromo-1H-pirrolo[2,3-b]piridina (**20**) en nitrometano o un solvente apropiado se agrega una cantidad apropiada de aluminio tricloruro. La solución obtenida se agita a temperatura ambiente durante 1 a 48 horas (calentada en un baño de aceite de ser necesario). A esta mezcla se agrega seguidamente una cantidad apropiada de cloruro de benzoilo en nitrometano o un solvente apropiado. La mezcla de reacción se calienta en un baño de aceite durante 2 a 48 horas. Se mitiga la reacción con un solvente apropiado. El precipitado es recogido mediante filtración

y se purifica mediante cromatografía para proporcionar el compuesto **33.**

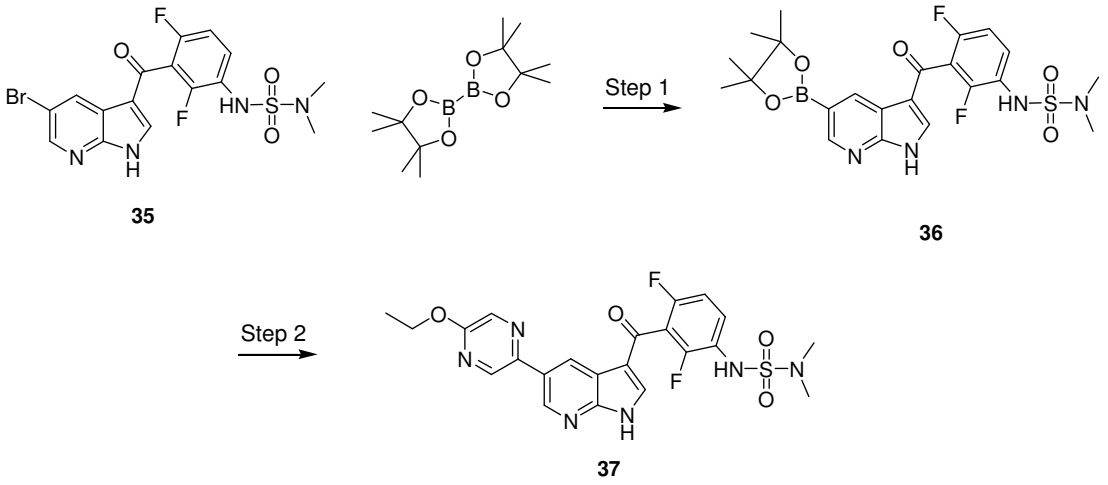
*Paso 2 – Preparación del compuesto **34:***

[0239] A una mezcla de compuesto **33,** un ácido borónico o un éster borónico apropiado y una cantidad apropiada de carbonato de cesio en 1,4-dioxano anhidroso o un solvente apropiado se agrega una cantidad apropiada de tetraquis(trifenilofosfina)paladio. Seguidamente se calienta la mezcla en un baño de aceite durante 2 a 48 horas. Después de enfriar hasta temperatura ambiente, se diluye la mezcla con etil acetato o un solvente apropiado, se filtra a través de celita y se concentra. Se purifica el residuo mediante cromatografía para proporcionar el compuesto **34.**

[0240] Cuando no hay ácido borónico o éster borónico comercialmente disponible, se prepara el ácido borónico o el éster del compuesto **33** siguiendo el procedimiento descrito en el Ejemplo 6, paso 4. Seguidamente se prepara el Compuesto **34** siguiendo el procedimiento mencionado anteriormente a partir de ácido borónico o éster del compuesto **33** y un haluro apropiado.

Ejemplo 9: Preparación de 3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-5-(5-etoxipiracin-2-il)-1H-pirrolo[2,3-b]piridina (37).

Esquema 9.



35 36 37

Paso 1.

[0241] En un vial de microondas se colocó 5-bromo-3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-1H-pirrolo[2,3-b]piridina **35** (70% puro, 200 mg, 0,3 mmol) con 4,4,5,5-tetrametil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (216,75 mg, 0,85 mmol) y se agregó acetato de potasio (100 mg, 1,02 mmol) seguido de complejo 1,1'-bis(difenilofosfino)ferroceno-paladio (II) dicloruro diclorometano (50 mg, 0,06 mmol). Se agregó 1,4-dioxano (3 mL) y la mezcla se irradió en reactor de microondas a 145 °C durante 45 minutos. La formación del producto intermedio **36** fue confirmada por LCMS. MS ESI [M+H+]+ = 506,95 [M-H+]- = 504,85.

Paso 2.

[0242] Se agregó 2-Bromo-5-etoxipiracina (200 mg, 0,99 mmol) en 1,5 mL de 1,4-dioxano a la mezcla de reacción, hecha en el paso 1, seguida de la adición de complejo de 1,1'-bis(difenilofosfino)ferroceno-paladio (II)dicloruro diclorometano (50 mg, 0,06 mmol) y 1M carbonato de potasio en agua (1,3

ml). Se irradió la reacción en reactor de microondas a 135°C durante 10 minutos. Después de enfriar la reacción, ésta fue colocada en salmuera y 1N HCl; la capa acuosa fue extraído con etil acetato. Se combinaron las capas orgánicas y se secaron con sulfato de sodio anhidroso. Después de retirar el agente de secado y el solvente, se purificó el residuo mediante cromatografía de gel de sílice y se eluyó con un gradiente de etil acetato: hexanos (10-100%) para proporcionar el 3-[3-(dimetilsulfamoilamino)-2,6-difluoro-benzoil]-5-(5-etoxipiracin-2-il)-1H-pirrolo[2,3-b]piridina **37** (16 mg, 10,2%). ESI [M+H+]+ = 503,0 [M-H+]- = 501,1.

Ejemplo 10: Propiedades del compuesto

[0243] Si bien la actividad inhibidora de los compuestos en cualquier Raf quinasa resulta importante para su actividad en el tratamiento de la enfermedad, los compuestos descritos en este documento muestran propiedades favorables que proporcionan ventajas también como producto farmacéutico.

[0244] Las pruebas para detectar actividad bioquímica y de base celular se conocen dentro de la tecnología, por ejemplo, las descritas en la publicación PCT WO 2007/002433, revelación que se incorpora al presente documento mediante referencia puesto que se relaciona con dichas pruebas. Por ejemplo, los valores de actividad bioquímica IC_{50} son determinados con respecto a la inhibición de la actividad de quinasa B-Raf V600E o la actividad de quinasa p-Erk, donde la inhibición de la fosforilación de un

sustrato de péptidos se mide como una función de la concentración de compuesto. Los compuestos a probar se diluyen en dimetil sulfóxido hasta una concentración de 0,1 mM. Éstos son diluidos en serie 15 µL en 30 µL de dimetil sulfóxido siete veces en placas de 96 cavidades para un total de 8 puntos de dilución y por cada punto de dilución se agrega 1 µL a una cavidad de una placa de prueba. Las placas se preparan de modo que cada cavidad en una placa de 384 cavidades contiene 1 µL de compuesto en un volumen de 10 µL con 0,1 ng enzima Raf (es decir, cualquiera de B-Raf, c-Raf-1 o B-Raf V600E, Upstate Biotechnology o se preparan mediante métodos conocidos por las personas capacitadas en la tecnología), 50 mM HEPES, pH 7,0, 50 mM NaCl, 2 mM $MgCl_2$, 1 mM $MnCl_2$, 0,01% Tween-20, 1 mM DTT y 100 nM biotin-MEK1 como sustrato. Se inicia la reacción con la adición de 10 µL de 200 µM ATP (es decir, 100 µM ATP final). Después de la incubación de la reacción de quinasa durante 45 minutos a temperatura ambiente, se agregan 5 µL/cavidad de solución de parada (25 mM Hepes pH 7,5, 100 mM EDTA, 0,01% BSA con nanoesferas donantes (nanoesferas recubiertas de estreptavidina, Perkin Elmer), nanoesferas receptoras (recubierta de proteína A, Perkin Elmer) y anticuerpo MEK1/2 Antic fósforo (CellSignal), cada una a una concentración final de 10 µg/mL). Las placas se incuban durante 3 horas a temperatura ambiente y se leen en un lector Envision (Perkin Elmer). La fosforilación de Mek1 conduce a la unión del anticuerpo anti-fosfor-MEK1/2 y vinculación de las nanoesferas donantes y recep-

toras de modo que la señal se correlacione con la actividad de quinasa. La concentración de señal contra compuesto se usa para determinar IC_{50}.

[0245] Los compuestos se evalúan a través de una diversidad de pruebas con base celular. Por ejemplo las líneas celulares humanas con mutación B-Raf V600E (melanoma A375, melanoma SKMEL3 y adenocarcinoma de colon COLO205), así como líneas celulares tumorigénicas con mutaciones B-RAF tipo salvaje (adenocarcinoma de colon SW620) o con mutaciones Ras (melanoma SKMEL2 y melanoma IPC298). Se pueden usar pruebas semejantes para evaluar líneas celulares tumorigénicas adicionales con mutaciones Ras, incluyendo, aunque no taxativamente, M202, M207, M243, M244, M296, S117, HCT116, HCT15, DLD1, MiaPaCa, A549, NCI-H23, NCI-H460, HOP62, MDA-MB231, Hs-578T, HL60, MOLT-4 y CCRF-CEM.

[0246] El Día 1 se cuentan las células, seguidamente se centrifugan en un tubo cónico durante 5 minutos a 1000 rpm. Se retira el sobrenadante y vuelven a suspenderse las células según se indica a continuación:

SW620 (catalogo ATCC No. CCL-27): resuspensión en medio L-15 de Leibovitz, 2 mM L-glutamina, 10% suero bovino fetal a 6 X 10^4 células/mL.

A375 (catálogo ATCC No. CRL-1619): resuspensión en medio de Eagle modificado de Dulbecco, 4 mM L-glutamina, 4,5 g/L D-glucosa, 10% suero bovino fetal a 6 X 10^4 células/mL.

COLO205 (catálogo ATCC No. CCL-222): resuspensión en RPMI

1640, 2 mM L-glutamina, 1,5 g/L bicarbonato de sodio, 4,5 g/L D-glucosa, 10 mM HEPES, 1,0 mM piruvato de sodio, 10% suero bovino fetal a 6 X 10^4 células/mL.

SKMEL2 (catálogo ATCC No. HTB-68): resuspensión en medio esencial de Eagle mínimo, 2 mM L-glutamina, 1,5 g/L bicarbonato de sodio, 0,1 mM aminoácidos no esenciales, 1,0 mM piruvato de sodio, 10% suero bovino fetal a 6 X 10^4 células/mL.

SKMEL3 (catálogo ATCC No. HTB-69): resuspensión en medio 5A de McCoy, 1,5 mM L-glutamina, 15% suero bovino fetal a 6 X 10^4 células/mL.

IPC298 (catálogo DSMZ No. ACC 251): resuspensión en RPMI 1640, 2 mM L-glutamina, 10% suero bovino fetal a 6 X 10^4 células/mL.

[0247] Se colocan las células en placas, 50 µL en cada cavidad de una placa de 96 cavidades (Corning 3610) y se incuban a 37 ^{o}C en 5% CO_2 de un día para otro, se colocan las células en una placa hasta una concentración final de células según se indica:

SW620: 5,000 células por cavidad.

A375: 2,000 células por cavidad.

COLO205: 2,000 células por cavidad.

SKMEL2: 2,000 células por cavidad.

SKMEL3: 3,000 células por cavidad.

IPC298: 2,000 células por cavidad.

[0248] El Día 2, el compuesto a una concentración máxima de 5 mM es diluido en serie 1:3 (p.ej. 10 µL con 30 µL dimetil sulfóxido) para un total de titulación de 8 puntos con DMSO como control. Se agrega una alícuota de 1 µL de cada punto de dilución y control a 249 µL de medio de cultivo y 50 µL a una cavidad que contiene células, proporcionando 10 µM de compuesto al máximo punto de concentración. Las células se incuban durante 3 días a 37 ^{o}C en 5% CO_2.

[0249] El Día 5, se lleva ATPlite 1 paso Sistema de Pruebas de Luminescencia (Perkin Elmer # 6016739) hasta temperatura ambiente junto con los cultivos celulares. Se agrega 25 µL ATPlite a cada cavidad, se agita durante 2 minutos y se incuban las células a temperatura ambiente durante 10 minutos, seguidamente se lee luminescencia en un lector Safire. La luminescencia medida se correlaciona directamente con el número de células, de modo que la lectura como una función de la concentración del compuesto concentración sirve para determinar el valor IC_{50}.

[0250] B9 es una línea celular de carcinoma de células escamosas que expresan HRAS activado aislado de un modelo de ratón inducido por DMBA/TPA de carcinogénesis de la piel (Stoler, et al. *The Journal of Cell Biology*, 1993, *122*(5), 1103-17). IPC-298 es una línea celular de melanoma humano que expresa NRAS activado (Aubert, et al. *International Journal of Cancer* 1993, *54*(5), 784-92). Para determinar si los compuestos inducen ERK y MEK fosforilado, las células se colocan en placas, en un plato

de 96 cavidades y se tratan con una titulación de 8 puntos de compuesto durante una hora a 37 °C. Seguidamente se retiran los medios y se incuban las células con solución reguladora de lisis que contiene inhibidores de proteasa y fosfatasa. ERK y MEK fosforilado en los lisatos obtenidos se detectan usando tecnología AlfaScreen™. Para detectar ERK fosforilado, se incuban los lisados celulares con nanoesferas donantes cubiertas con estreptavidina, nanoesferas receptoras de IgG antirratón, un anticuerpo de conejo anti-ERK1/2 conejo biotinilado y un anticuerpo de ratón que reconoce a ERK1/2 únicamente cuando éste es fosforilado en Thr202 y Tyr204. El anticuerpo biotinilado ERK1/2 se une tanto a las nanoesferas donantes recubiertas de estreptavidina como a ERK1/2 (sin importar su estado de fosforilación) y el anticuerpo fosfo-ERK1/2 se une a las nanoesferas receptoras y aERK1/2 fosforilado en Thr202/Tyr204. La excitación de las nanoesferas con láser luminoso a 680 nm produce oxígeno singlete, el cual se mitiga rápidamente salvo que las nanoesferas estén a una distancia corta. Cuando se fosforila ERK, ambos anticuerpos pueden unirse a la misma proteína, llevando las nanoesferas donante y receptora a una distancia corta, produciendo una señal que puede medirse a 580 nm. La fosforilación MEK es detectada usando un enfoque semejante, únicamente con anticuerpo dirigidos contra MEK1/2 y MEK1/2 total fosforilado en Ser217 y Ser221.

[0251] Queda entendido que los resultados de estas pruebas pueden variar de varias las condiciones de dichas pruebas. Los

niveles de inhibición determinados en las condiciones descritas en este documento representan una actividad relativa para los compuestos probadas en condiciones específicas usadas. Las pruebas con base de células probablemente mostrarán variabilidad debido a la complejidad del sistema y la sensibilidad del mismo frente a cualquier cambio en las condiciones de prueba. Como tal, cierto nivel de inhibición en las pruebas con base de células es indicativo de los compuestos que tienen cierta actividad inhibidora para aquellas células, en tanto que la falta de inhibición por debajo del umbral de la concentración más alta probada no indica necesariamente que el compuesto no posee actividad sobre las células, únicamente que en las condiciones probadas, no se observa inhibición. En algunos casos, los compuestos no fueron probados en todas las pruebas o los resultados de las pruebas no fueron válidos, según se indica como NA en las tablas siguientes.

[0252] La tabla siguiente proporciona datos que indican la actividad de activación celular de B-Raf V600E y IPC-298_P-ERK, la actividad inhibidora del crecimiento celular de A375_P-ERK y COLO205 para compuestos ejemplo según se describen en este documento:

Número del compuesto	Actividad bioquímica (IC_{50} µM)	Actividad celular (EC_{50} µM)	Actividad celular (IC_{50} µM)

	V600E	IPC-298_P-ERK	A375	COLO205
P-0012	< 0,1	> 10	< 1	> 1
P-0013	< 0,1	> 10	< 1	> 1
P-0014	< 0,1	> 8	< 1	< 1
P-0015	< 0,1	> 10	< 1	> 1
P-0016	< 0,1	NA	< 1	< 1
P-0017	< 0,1	> 10	< 1	> 1
P-0018	< 0,1	> 10	< 1	> 1
P-0019	< 0,1	> 10	< 1	> 1
P-0020	< 0,1	> 10	< 1	< 1
P-0021	< 0,1	> 10	< 1	< 1
P-0022	< 0,1	> 10	< 1	< 1
P-0023	< 0,1	> 10	< 1	> 1
P-0024	< 0,1	> 10	< 1	> 1
P-0025	< 0,1	> 10	< 1	< 1
P-0026	> 0,1	> 10	> 1	
P-0027	< 0,1	NA	< 1	< 1
P-0028	< 0,1	> 10	< 1	< 1
P-0029	< 0,1	> 10	< 1	< 1
P-0030	< 0,1	> 10	< 1	< 1
P-0031	< 0,1	> 10	< 1	< 1
P-0032	< 0,1	> 10	< 1	< 1
P-0033	< 0,1	> 10	< 1	< 1
P-0034	< 0,1	> 10	< 1	> 1

Número del compuesto	Actividad bioquímica (IC_{50} µM)	Actividad celular (EC_{50} µM)	Actividad celular (IC_{50} µM)	
	V600E	IPC-298_P-ERK	A375	COLO205
P-0035	< 0,1	> 10	< 1	> 1
P-0036	< 0,1	> 10	< 1	> 1
P-0037	< 0,1	> 10	< 1	> 1
P-0038	< 0,1	> 10	< 1	> 1
P-0039	< 0,1	> 10	< 1	> 1
P-0040	< 0,1	> 10	< 1	< 1
P-0041	> 0,1	> 10	> 1	
P-0042	< 0,1	> 10	< 1	< 1
P-0043	< 0,1	> 10	< 1	< 1
P-0044	< 0,1	> 10	< 1	< 1
P-0045	< 0,1	> 10	< 1	< 1
P-0046	< 0,1	> 10	< 1	< 1
P-0047	< 0,1	> 10	< 1	< 1
P-0048	< 0,1	> 10		< 1
P-0049	< 0,1	> 4	< 1	< 1
P-0050	< 0,1	> 10	< 1	< 1
P-0051	< 0,1	> 10	< 1	< 1
P-0052	< 0,1	> 10	< 1	< 1
P-0053	< 0,1	> 10	< 1	< 1
P-0054	< 0,1	> 1	< 1	> 1

Número del compuesto	Actividad bioquímica (IC_{50} µM)	Actividad celular (EC_{50} µM)	Actividad celular (IC_{50} µM)	
	V600E	IPC-298_P-ERK	A375	COLO205
P-0055	< 0,1	> 10	< 1	< 1
P-0056	< 0,1	> 10	< 1	< 1
P-0057	< 0,1	> 10	< 1	< 1
P-0058	< 0,1	> 10	< 1	< 1
P-0059	< 0,1	> 10	< 1	< 1
P-0060	< 0,1	> 2	< 1	< 1
P-0061	< 0,1	> 10	< 1	< 1
P-0062	< 0,1	> 10	< 1	< 1
P-0063	< 0,1	> 10	< 1	< 1
P-0064	< 0,1	> 10	< 1	< 1
P-0065	< 0,1		< 1	> 1
P-0066	< 0,1		< 1	< 1
P-0067	< 0,1		< 1	> 1
P-0068	< 0,1			
P-0069	< 0,1			
P-0070	> 0,1		< 1	> 1
P-0071	> 0,1		< 1	> 1
P-0072	> 0,1		< 1	> 1
P-0073	> 0,1		< 1	> 1
P-0074	> 0,1		< 1	> 1

Número del compuesto	Actividad bioquímica (IC_{50} µM)	Actividad celular (EC_{50} µM)	Actividad celular (IC_{50} µM)	
	V600E	IPC-298_P-ERK	A375	COLO205
P-0075	> 0,1		< 1	> 1
P-0076	< 0,1		< 1	< 1
P-0077	< 0,1		< 1	< 1
P-0078	< 0,1		< 1	> 1
P-0079	< 0,1		< 1	< 1
P-0080	< 0,1		< 1	> 1
P-0081	< 0,1		< 1	< 1
P-0082	< 0,1		< 1	< 1
P-0083	< 0,1		< 1	< 1
P-0084	< 0,1		< 1	< 1
P-0085	< 0,1		< 1	> 1
P-0086	< 0,1		< 1	< 1
P-0087	< 0,1		< 1	< 1
P-0088	< 0,1		< 1	> 1
P-0089	< 0,1		< 1	> 1
P-0090	< 0,1		< 1	< 1
P-0091	< 0,1		< 1	< 1
P-0092	< 0,1		< 1	< 1
P-0093	< 0,1		< 1	< 1
P-0094	< 0,1		< 1	< 1

Número del compuesto	Actividad bioquímica (IC_{50} µM)	Actividad celular (EC_{50} µM)	Actividad celular (IC_{50} µM)	
	V600E	IPC-298_P-ERK	A375	COLO205
P-0095	< 0,1		< 1	< 1
P-0096	< 0,1		< 1	< 1
P-0097	< 0,1		< 1	< 1
P-0098	< 0,1		< 1	< 1
P-0099	< 0,1		< 1	> 1
P-0100	< 0,1		< 1	> 1
P-0101	< 0,1		< 1	> 1
P-0102	< 0,1		< 1	> 1
P-0103	< 0,1		< 1	< 1
P-0104	< 0,1		< 1	< 1
P-0105	< 0,1		< 1	< 1
P-0106	< 0,1		< 1	< 1
P-0107	< 0,1		< 1	< 1
P-0108	< 0,1		< 1	> 1
P-0109	< 0,1		< 1	< 1
P-0235	< 0,1		< 1	< 1
P-0236	< 0,1		< 1	< 1
P-0237	< 0,1		< 1	< 1
P-0238	< 0,1		< 1	< 1
P-0239	< 0,1		< 1	< 1

Número del compuesto	Actividad bioquímica (IC_{50} µM)	Actividad celular (EC_{50} µM)	Actividad celular (IC_{50} µM)	
	V600E	IPC-298_P-ERK	A375	COLO205
P-0240	< 0,1		< 1	< 1
P-0241	< 0,1		< 1	< 1
P-0242	< 0,1		> 1	> 1
P-0243	< 0,1		> 1	> 1
P-0244	< 0,1		> 1	> 1
P-0245	< 0,1		< 1	< 1
P-0246	< 0,1		> 1	> 1
P-0247	< 0,1		< 1	< 1
P-0248	< 0,1		< 1	< 1
P-0249	< 0,1		< 1	< 1
P-0251	< 0,1		> 1	> 1
P-0252	< 0,1		< 1	< 1
P-0253	< 0,1		> 1	> 1
P-0254	< 0,1		< 1	< 1
P-0255	< 0,1		< 1	< 1
P-0256	< 0,1		< 1	< 1
P-0257	> 0,1			> 1
P-0258	< 0,1		< 1	< 1
P-0259	< 0,1		< 1	< 1
P-0260	< 0,1		< 1	< 1

Número del compuesto	Actividad bioquímica (IC_{50} µM)	Actividad celular (EC_{50} µM)	Actividad celular (IC_{50} µM)	
	V600E	IPC-298_P-ERK	A375	COLO205
P-0261	< 0,1		< 1	< 1
P-0262	< 0,1		< 1	< 1
P-0263	< 0,1		< 1	< 1
P-0264	< 0,1		< 1	< 1
P-0265	< 0,1	> 2	< 1	< 1
P-0266	< 0,1		< 1	< 1
P-0267	> 0,1			
P-0268	< 0,1		< 1	< 1
P-0269	< 0,1		< 1	< 1
P-0270	< 0,1		< 1	< 1
P-0271	< 0,1		< 1	< 1
P-0272	> 0,1			
P-0273			< 1	< 1
P-0274	< 0,1		< 1	> 1
P-0275	< 0,1		< 1	< 1
P-0276	< 0,1		< 1	> 1
P-0277	> 0,1		< 1	< 1
P-0279	< 0,1		> 1	< 1
P-0280			< 1	< 1
P-0281	< 0,1		< 1	< 1

Número del compuesto	Actividad bioquímica (IC_{50} µM)	Actividad celular (EC_{50} µM)	Actividad celular (IC_{50} µM)	
	V600E	IPC-298_P-ERK	A375	COLO205
P-0282	< 0,1		< 1	< 1
P-0283	< 0,1		> 1	< 1
P-0284			< 1	< 1
P-0285	< 0,1		< 1	< 1
P-0286	< 0,1		> 1	< 1
P-0287		> 4	< 1	< 1
P-0288	< 0,1	> 2	< 1	< 1
P-0289	< 0,1		< 1	< 1
P-0291	> 0,1			
P-0292			< 1	< 1
P-0293	< 0,1		< 1	< 1
P-0294	< 0,1		> 1	> 1
P-0295	< 0,1	> 2	< 1	< 1
P-0297	< 0,1		> 1	> 1
P-0298	< 0,1		> 1	> 1
P-0299	< 0,1		> 1	> 1
P-0300	< 0,1	> 4	< 1	> 1
P-0301	< 0,1		< 1	> 1
P-0302	< 0,1		< 1	< 1
P-0303	< 0,1		> 1	> 1

Número del compuesto	Actividad bioquímica (IC_{50} µM)	Actividad celular (EC_{50} µM)	Actividad celular (IC_{50} µM)	
	V600E	IPC-298_P-ERK	A375	COLO205
P-0304	< 0,1		< 1	< 1
P-0305	< 0,1		< 1	< 1
P-0306	< 0,1		> 1	< 1
P-0307	< 0,1		< 1	< 1
P-0308	< 0,1		< 1	< 1
P-0309	< 0,1		< 1	< 1
P-0310	< 0,1		< 1	< 1
P-0311	< 0,1		< 1	< 1
P-0312	< 0,1		< 1	< 1
P-0313	< 0,1		< 1	< 1
P-0314	< 0,1		< 1	< 1
P-0315	< 0,1		< 1	< 1
P-0316	< 0,1		< 1	< 1
P-0317	< 0,1		< 1	< 1
P-0318	< 0,1		< 1	< 1
P-0319	< 0,1		< 1	< 1
P-0320	> 0,1			
P-0321	< 0,1		< 1	< 1
P-0322	< 0,1		< 1	< 1
P-0324	< 0,1		< 1	< 1

Número del compuesto	Actividad bioquímica (IC_{50} µM)	Actividad celular (EC_{50} µM)	Actividad celular (IC_{50} µM)	
	V600E	IPC-298_P-ERK	A375	COLO205
P-0325	< 0,1		< 1	> 1
P-0326	< 0,1		> 1	> 1
P-0327	< 0,1		< 1	< 1
P-0334	< 0,1	> 2	> 1	> 1
P-0335	< 0,1		< 1	< 1
P-0336	> 0,1	> 4		
P-0337	< 0,1		> 1	> 1
P-0338	< 0,1		< 1	< 1
P-0339	< 0,1		< 1	< 1
P-0340	< 0,1		< 1	< 1
P-0223	> 0,1			
P-0224	< 0,1		< 1	< 1
P-0225	< 0,1		< 1	< 1
P-0226	< 0,1		< 1	< 1
P-0227	< 0,1		< 1	< 1
P-0228	< 0,1		< 1	< 1
P-0229	< 0,1		< 1	< 1
P-0230	< 0,1		< 1	< 1
P-0231	< 0,1		< 1	< 1
P-0232	< 0,1		< 1	< 1

Número del compuesto	Actividad bioquímica (IC_{50} µM)	Actividad celular (EC_{50} µM)	Actividad celular (IC_{50} µM)	
	V600E	IPC-298_P-ERK	A375	COLO205
P-0233	< 0,1		> 1	> 1
P-0117	> 0,1		> 1	> 1
P-0116	< 0,1		< 1	< 1
P-0115	< 0,1		< 1	< 1
P-0114	< 0,1		< 1	< 1
P-0113	< 0,1		< 1	< 1
P-0112	< 0,1		< 1	< 1
P-0111	< 0,1		< 1	< 1
P-0110	< 0,1		< 1	< 1

[0253] La tabla siguiente proporciona datos de la actividad de activación celular de IPC-298_P-ERK, la actividad inhibidora del crecimiento celular de A375_P-ERK y COLO205 para algunos compuestos ejemplo conocidos dentro de la tecnología.

Compuesto	Actividad celular (EC_{50} µM)	Actividad celular (IC_{50} µM)	
	IPC-298_P-ERK	A375	COLO205
N-[3-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonilo)-2,4-	< 0,5	< 0,8	< 1

difluoro-fenilo]propano-1-sulfonamida			
N-[2,4-difluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]-2-fluoro-bencenosulfonamida	< 0,5	< 0,5	< 1
N-[2,4-difluoro-3-[5-(2-metoxipirimidin-5-il)-1H-pirrolo[2,3-b]piridina-3-carbonilo]fenilo]-2,5-difluoro-bencenosulfonamida	< 1	< 0,5	< 1

[0254] Las propiedades farmacocinéticas de los compuestos (incluyendo cualquier forma sólida o formulaciones de los mismos) se evalúan en ratas machos Sprague Dawley o perros machos Beagle. Se administra a las ratas dosis diarias del compuesto o bien a través de inyecciones IV por medio de catéteres yugulares colocados quirúrgicamente o por alimentación oral forzada (PO). Se prepara cada compuesto como una solución madre de 20 mg/mL en dimetil sulfóxido, el cual es diluido adicionalmente para proporcionar la solución madre de dosificación en la concentración deseada para las formulaciones IV o PO. Para dosificación IV, la solución madre de dosificación se diluye en una mezcla 1:1:8 de Solutol ®:etanol:agua. Para dosificación PO, la solución madre de dosificación se diluye en una metilcelulosa 1%. En un formato

de casete (o cada compuesto, forma sólida del mismo o formulación del mismo hecha individualmente), se diluyen los compuestos hasta 0,5 mg/mL cada uno para la dosificación IV y 0,4 mg/mL cada una para la dosificación PO y se dosifican a 1 mg/kg (2mL/kg) o 2 mg/kg (5 mL/kg), respectivamente. Para animales dosificados IV, se recogen muestras de sangre venosa de la cola con anticoagulante de heparina de litio a 5, 15, 30 y 60 minutos y 4, 8 y 24 horas posterior a la dosis cada día. Para animales dosificados con PO, se recogen las muestras de sangre venosa de la cola con anticoagulante de heparina de litio a los 30 minutos, 1, 2, 4, 8 y 24 horas posterior a la dosificación cada día. Los perros reciben dosis diarias en cápsulas orales con una formulación adecuada de 50 mg/mL. Se recogen muestras sanguíneas de la vena cefálica con anticoagulante de heparina de litio a los 30 minutos, 1, 2, 4, 8 y 24 horas posterior a la dosificación de cada día. Se procesan todas las muestras hasta el plasma y se congelan para el análisis posterior de cada compuesto mediante LC/MS/MS. Se grafican los niveles plasmáticos como una función del tiempo para evaluar AUC (ng*hr/mL). Los compuestos de conformidad con la presente invención preferiblemente muestran propiedades farmacocinéticas mejoradas en relación con compuestos descritos previamente, es decir, tienen valores considerablemente más altos para una o más AUC, Cmax y vida media en relación con compuestos descritos previamente.

[0255] Todas las patentes, solicitudes de patente y demás re-

ferencias citadas en la especificación son indicativas del nivel de destreza de las personas capacitadas en la tecnología a la cual pertenece la invención y quedan incorporadas mediante referencia en su totalidad, incluyendo cualquier tabla y cifra, en la misma medida que cada referencia hubiera sido incorporada mediante referencia en su totalidad de manera individual.

[0256] Una persona capacitada en la tecnología podrá apreciar rápidamente que la presente invención ha sido bien adaptada para alcanzar los fines y ventajas mencionados, así como aquellos inherentes a la misma. Los métodos, variaciones y composiciones descritas en este documento como representativos actualmente de realizaciones preferidas son ejemplos y no reflejan taxativamente el alcance de la invención. Las personas capacitadas en la tecnología pueden proponer cambios y otros usos, comprendidos dentro del espíritu de la invención y definidos por el alcance de las reivindicaciones.

[0257] En tanto que esta invención ha sido revelada con referencia a realizaciones específicas, es obvio que las personas capacitadas en la tecnología pueden diseñar otras realizaciones y variaciones de la presente invención sin desviarse del verdadero espíritu y alcance de la invención.

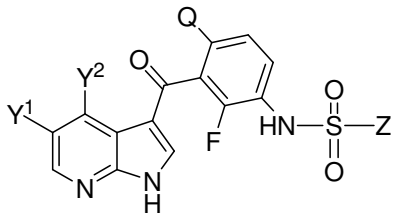
[0258] Adicionalmente, cada vez que se describen características o aspectos de la invención en términos de grupos Markush u otros grupos de alternativas, las personas capacitadas en tecnología sabrán reconocer que la invención es descrita también en

este documento en términos de cualquier miembro individual o subgrupo de miembros del grupo Markush u otro grupo.

[0259] Asimismo, salvo que se indique lo contrario, cada vez que se proporcionen diversos valores numéricos par alas realizaciones, se describen realizaciones adicionales tomando cualesquiera dos valores diferentes como puntos finales de una gama. Dichas gamas también están dentro del alcance de la invención descrita.

REIVINDICACIONES

Un compuesto de fórmula I:



I

o sales, hidratos, solvatos, tautómeros e isómeros de los mismos aceptables farmacéuticamente;

donde:

Y^1 se selecciona del grupo que consiste en CN, halógeno, -OH, C_{1-6} alquilo sustituido opcionalmente, C_{1-6} alcoxi sustituido opcionalmente, C_{3-6}cicloalquilo sustituido opcionalmente, C_{1-6}haloalquilo sustituido opcionalmente, C_{1-6}haloalcoxi sustituido opcionalmente, arilo sustituido opcionalmente y heteroarilo sustituido opcionalmente; opcionalmente donde los dos sustituyentes adyacentes en el anillo de arilo o heteroarilo junto con los átomos a los cuales están unidos forman un anillo de 5 o 6 miembros sustituido opcionalmente que tiene de 0 a 3 heteroátomos adicionales seleccionados de N, O o S;

Y^2 es H, halógeno, CN, C_{1-6}alquilo, C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, C_{3-8}cicloalquilo-C_{0-4}alquilo o $(R^2)(R^3)$ N-, donde R^2 y R^3 son seleccionados cada uno por separado del grupo

que consiste en H, C_{1-6}alquilo, C_{1-6}alcoxi, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, C_{3-8}cicloalquilo-C_{0-4}alquilo, heterocicloalquilo y heterocicloalquilo-C_{1-4}alquilo; o R^2 y R^3 tomados junto con el átomo de nitrógeno al cual están unidos forman un anillo de tres a ocho miembros que tiene de 0-2 heteroátomos adicionales como miembros de anillo seleccionados de N, O o S; donde Y^2 es sustituido opcionalmente con uno a tres grupos seleccionados por separado de R^e;

Q es seleccionado de H, F, Cl o CH_3;

Z es $-N(R^4)(R^5)$ o $-C(R^6)(R^7)(R^8)$, donde

R^4 y R^5 son seleccionados cada uno por separado del grupo que consiste en H, C_{1-6}alquilo sustituido opcionalmente, C_{3-8}cicloalquilo sustituido opcionalmente, C_{3-8}cicloalquiloalquilo sustituido opcionalmente, heterocicloalquilo sustituido opcionalmente, heterocicloalquiloalquilo sustituido opcionalmente, arilo sustituido opcionalmente, ariloalquilo sustituido opcionalmente, heteroarilo sustituido opcionalmente y heteroariloalquilo sustituido opcionalmente; o

R^4 y R^5 tomados junto con el átomo de nitrógeno al cual están unidos forman un anillo de cuatro a ocho miembros que tiene de 0-2 heteroátomos adicionales como miembros de anillo seleccionados de N, O o S, donde el anillo de cuatro a ocho miembros es sustituido opcionalmente;

R^6, R^7 y R^8 son cada uno por separado H, C_{1-6}alquilo , sustituido opcionalmente, C_{1-6}haloalquilo sustituido opcionalmen-

te, C_{1-6}haloalcoxi sustituido opcionalmente, C_{3-8}cicloalquilo sustituido opcionalmente, C_{3-8}cicloalquiloalquilo sustituido opcionalmente, arilo sustituido opcionalmente, ariloalquilo sustituido opcionalmente, heterocicloalquilo sustituido opcionalmente, heterocicloalquiloalquilo sustituido opcionalmente, heteroarilo sustituido opcionalmente, heteroariloalquilo sustituido opcionalmente o $-X^2R^9$, donde X^2 es $-NR^{10}$, O o S; R^{10} es H, C_{1-6}alquilo o arilo; y R^9 es H, C_{1-6}alquilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo o heteroariloalquilo, donde R^9 es sustituido opcionalmente con 1 a 3 sustituyentes R^e; o dos opciones cualesquiera de los grupos R^6, R^7 y R^8 grupos tomados junto con el átomo de carbono al cual están unidos forma un anillo no aromático de 3 a 8 miembros sustituido opcionalmente que tiene de 0 a 2 heteroátomos seleccionados de N, O o S; proporcionado en cada aparición, como mínimo dos opciones cualesquiera de los grupos R^6, R^7 y R^8 no son simultáneamente hidrógeno; y

en el entendido de que cuando (i) Y^1 es halógeno, $-CH_3$, –CN, –OMe o 2–metoxipirimidin–5–il, Z es otro aparte de dimetilamino, dietilamino, 1–pirrolodina, 1–piperidinilo, 4–morfolinilo, isopropilo, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_3)(CH_2CH_2CH_3)$, ciclobutilo, ciclopentilo o ciclohexilo; y (ii) cuando Y^1 es 1–metil–4–pirazolilo, 3–metilsulfonilfenilo o 3–metilsulfonilaminofenilo, Z es otro aparte de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo.

1. El compuesto de la Reivindicación **1**, donde

Y^1 es CN, halógeno, –OH, C_{1-6} alquilo, C_{1-6} alcoxi, C_{3-6}cicloalquilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, arilo y heteroarilo sustituido opcionalmente, donde la porción alifática o aromática de Y^1 es cada una por separado sustituida opcionalmente con 1–5 R^1 sustituyentes; cada R^1 es seleccionado por separado de C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquilo–C_{1-4}–alquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, heterocicloalquilo, heterocicloalquilo–C_{1-4}alquilo o $-R^a$, donde R^a es seleccionado de halógeno, $-CH=CH_2$, –CN, –OH, $-NH_2$, $-NO_2$, $-C(O)OH$, $-C(S)OH$, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^b$, $-SR^b$, $-OC(O)R^b$, $-OC(S)R^b$, $-C(O)R^b$, $-C(S)R^b$, $-C(O)OR^b$, $-C(S)OR^b$, $-S(O)R^b$, $-S(O)_2R^b$, $-C(O)NHR^b$, $-C(S)NHR^b$, $-C(O)NR^bR^b$, $-C(S)NR^bR^b$, $-S(O)_2NHR^b$, $-S(O)_2NR^bR^b$, $-C(NH)NHR^b$, $-C(NH)NR^bR^b$, $-NHC(O)R^b$, $-NHC(S)R^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NHS(O)_2R^b$, $-NR^bS(O)_2R^b$, $-NHC(O)NHR^b$, $-NHC(S)NHR^b$, $-NR^bC(O)NH_2$, $-NR^bC(S)NH_2$, $-NR^bC(O)NHR^b$, $-NR^bC(S)NHR^b$, $-NHC(O)NR^bR^b$, $-NHC(S)NR^bR^b$, $-NR^bC(O)NR^bR^b$, $-NR^bC(S)NR^bR^b$, $-NHS(O)_2NHR^b$, $-NR^bS(O)_2NH_2$, $-NR^bS(O)_2NHR^b$, $-NHS(O)_2NR^bR^b$, $-NR^bS(O)_2NR^bR^b$, $-NHR^b$ o $-NR^bR^b$, donde cada R^b es seleccionado por separado del grupo que consiste en C_{1-6}alquilo, halógeno, –CN, C_{1-6}alcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquilo–C_{1-4}–alquilo, –OH, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, arilo, arilo–C_{1-4}alquilo, heteroarilo y heteroariloalquilo; o dos sustituyentes R^b cuando están unidos al mismo átomo de nitrógeno

tomados junto con el átomo de nitrógeno forman un anillo de tres a ocho miembros que tiene de 0–2 heteroátomos adicionales como miembros de anillo seleccionados de N, O o S; donde la porción alifática o aromática de R^1 es sustituida opcionalmente además con 1–3 grupos seleccionados de C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, heterocicloalquilo, heterocicloalquilo–C_{1-4}alquilo o $-R^c$, donde cada R^c es seleccionado por separado de halógeno, $-CH=CH_2$, $-CN$, $-OH$, $-NH_2$, $-NO_2$, $-C(O)OH$, $-C(S)OH$, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^d$, $-SR^d$, $-OC(O)R^d$, $-OC(S)R^d$, $-C(O)R^d$, $-C(S)R^d$, $-C(O)OR^d$, $-C(S)OR^d$, $-S(O)R^d$, $-S(O)_2R^d$, $-C(O)NHR^d$, $-C(S)NHR^d$, $-C(O)NR^dR^d$, $-C(S)NR^dR^d$, $-S(O)_2NHR^d$, $-S(O)_2NR^dR^d$, $-C(NH)NHR^d$, $-C(NH)NR^dR^d$, $-NHC(O)R^d$, $-NHC(S)R^d$, $-NR^dC(O)R^d$, $-NR^dC(S)R^d$, $-NHS(O)_2R^d$, $-NR^dS(O)_2R^d$, $-NHC(O)NHR^d$, $-NHC(S)NHR^d$, $-NR^dC(O)NH_2$, $-NR^dC(S)NH_2$, $-NR^dC(O)NHR^d$, $-NR^dC(S)NHR^d$, $-NHC(O)NR^dR^d$, $-NHC(S)NR^dR^d$, $-NR^dC(O)NR^dR^d$, $-NR^dC(S)NR^dR^d$, $-NHS(O)_2NHR^d$, $-NR^dS(O)_2NH_2$, $-NR^dS(O)_2NHR^d$, $-NHS(O)_2NR^dR^d$, $-NR^dS(O)_2NR^dR^d$, $-NHR^d$, R^f o $-NR^dR^d$, donde cada R^d es seleccionado por separado de C_{1-6}alquilo, arilo-alquilo, arilo, heteroarilo, heteroariloalquilo, cicloalquilo, cicloalquiloalquilo, heterocicloalquilo o heterocicloalquiloalquilo; y donde la porción aromática de R^1 es sustituido opcionalmente con 1–3 sustituyentes seleccionados por separado de R^e, donde R^e se selecciona del grupo que consiste en halógeno, $-CN$, $-CH=CH_2$, $-OH$, $-NH_2$, $-NO_2$, $-C(O)OH$, $-C(S)OH$, $-C(O)NH_2$, $-C(S)NH_2$,

$-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^f$, $-SR^f$, $-OC(O)R^f$, $-OC(S)R^f$, $-C(O)R^f$, $-C(S)R^f$, $-C(O)OR^f$, $-C(S)OR^f$, $-S(O)R^f$, $-S(O)_2R^f$, $-C(O)NHR^f$, $-C(S)NHR^f$, $-C(O)NR^fR^f$, $-C(S)NR^fR^f$, $-S(O)_2NHR^f$, $-S(O)_2NR^fR^f$, $-C(NH)NHR^f$, $-C(NH)NR^fR^f$, $-NHC(O)R^f$, $-NHC(S)R^f$, $-NR^fC(O)R^f$, $-NR^fC(S)R^f$, $-NHS(O)_2R^f$, $-NR^fS(O)_2R^f$, $-NHC(O)NHR^f$, $-NHC(S)NHR^f$, $-NR^fC(O)NH_2$, $-NR^fC(S)NH_2$, $-NR^fC(O)NHR^f$, $-NR^fC(S)NHR^f$, $-NHC(O)NR^fR^f$, $-NHC(S)NR^fR^f$, $-NR^fC(O)NR^fR^f$, $-NR^fC(S)NR^fR^f$, $-NHS(O)_2NHR^f$, $-NR^fS(O)_2NH_2$, $-NR^fS(O)_2NHR^f$, $-NHS(O)_2NR^fR^f$, $-NR^fS(O)_2NR^fR^f$, $-NHR^f$, $-NR^fR^f$ y R^f, donde R^f es C_{1-6}alquilo o arilo; o dos grupos adyacentes R^1 en el anillo de arilo o heteroarilo junto con los átomos a los cuales están unidos forman un anillo de 5 o 6 miembros que tiene de 0 a 2 heteroátomos adicionales seleccionados de N, O o S, sustituido opcionalmente con 1 a 3 sustituyentes R^d;

R^4 y R^5 son seleccionados cada uno por separado del grupo que consiste en H, C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, heterocicloalquilo, heterocicloalquiloalquilo, arilo, ariloalquilo, heteroarilo y heteroariloalquilo, donde R^4 o R^5 es sustituido opcionalmente con 1 a 3 miembros seleccionados por separado de C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, heterocicloalquilo, heterocicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo o R^c; o R^4 y R^5 tomados junto con el átomo de nitrógeno al cual están unidos forman un anillo de cuatro a ocho miembros que tiene de 0-2 heteroátomos

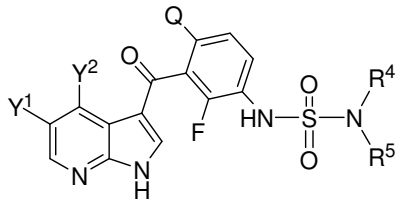
adicionales como miembros de anillo seleccionados de N, O o S, donde dicho anillo de cuatro a ocho miembros es sustituido opcionalmente con uno a tres grupos seleccionados por separado de C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo o R^e; y

R^6, R^7 y R^8 son cada uno por separado H, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, C_{3-8} cicloalquilo, C_{3-8} cicloalquiloalquilo, arilo, ariloalquilo, heterocicloalquilo, heterocicloalquiloalquilo, heteroarilo, heteroariloalquilo o $-X^2R^9$; donde la porción alifática o aromática de R^6, R^7 y R^8 es cada una sustituida opcionalmente con 1 a 3 miembros seleccionados por separado del grupo que consiste en C_{3-8} cicloalquilo, C_{3-8} cicloalquiloalquilo, arilo, ariloalquilo, heterocicloalquilo, heterocicloalquiloalquilo, heteroarilo, heteroariloalquilo y R^e; o dos opciones cualesquiera de los grupos R^6, R^7 y R^8 grupos tomados junto con el átomo de carbono al cual están unidos forman un anillo carbocíclico de 3 a 8 miembros o un anillo heterocíclico de 4 a 8 miembros que tiene de 1 a 2 heteroátomos como miembros de anillo seleccionados de N, O o S, donde el anillo carbocíclico de 3 a 8 miembros o el anillo heterocíclico de 4 a 8 miembros es sustituido opcionalmente con uno a tres grupos seleccionados por separado de C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{1-6}alquilo sustituido opcionalmente con R^e, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo o heteroariloalquilo o R^e.

2. El compuesto de la Reivindicación **2**, donde Y^1 es arilo o grupos heteroarilo, donde el grupo heteroarilo tiene de 1 a 4 heteroátomos como miembros de anillo seleccionados de N, O o S; y donde e arilo o grupos heteroarilo son sustituidos opcionalmente con 1 a 3 R^1 sustituyentes.

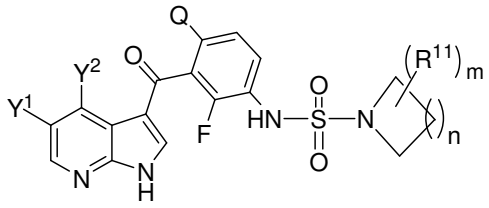
3. El compuesto de la Reivindicación **1**, donde Y^1 es CN, halógeno, –OH, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6}haloalquilo o C_{1-6}haloalcoxi.

4. El compuesto de la Reivindicación **1**, que tiene formula (Ia):



Ia.

5. El compuesto de la Reivindicación **1**, que tiene formula (Ib):



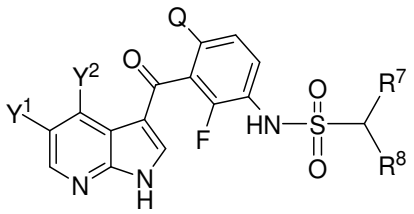
Ib

donde R^{11} es C_{1-6}alquilo, C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, heterocicloalquilo, heterocicloalquiloalquilo o R^e;

el subíndice m es un número entero de 0 a 3; y

el subíndice n es un número entero de 1 a 5.

6. El compuesto de la Reivindicación **1**, que tiene formula (Ic):



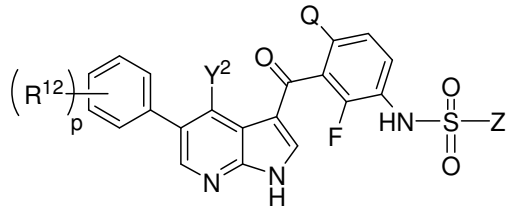
Ic

donde R^7 y R^8 son cada uno por separado C_{1-6}alquilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo o $-X^2R^9$, donde la porción alifática o aromática de R^7 y R^8 es cada una sustituida opcionalmente con 1 a 3 miembros seleccionados por separado del grupo que consiste en C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo y R^e, proporcionado en cada aparición, como mínimo dos opciones cualesquiera de los grupos R^6, R^7 y R^8 grupos no son simultáneamente hidrógeno; y donde X^2 es $-NR^{10}$, O o S; R^{10} es H, C_{1-6}alquilo o arilo; y R^9 es H, C_{1-6}alquilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo o heteroariloalquilo, donde R^9 es sustituido opcionalmente con 1 a 3 R^e sustituyentes; o

R^7 y R^8 grupos tomados junto con el átomo de carbono al cual están unidos forman un anillo carbocíclico de 3 a 8 miembros o un anillo heterocíclico de 4 a 8 miembros que tiene de 1 a 2 heteroátomos como miembros de anillo seleccionados de N, O o

S, donde el anillo carbocíclico de 3 a 8 miembros o el anillo heterocíclico de 4 a 8 miembros es sustituido opcionalmente con uno a tres grupos seleccionados por separado de C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo o heteroariloalquilo o R^e.

7. El compuesto de la Reivindicación **1,** que tiene formula (Id):



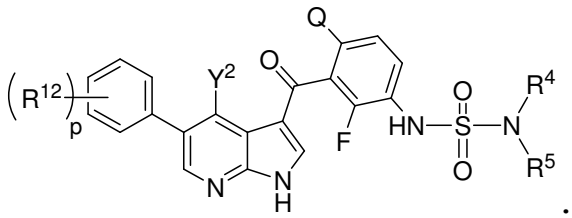
Id

donde:

R^{12} es H o R^1; o dos grupos adyacentes R^{12} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0–2 heteroátomos como miembros de anillo seleccionados de O, N o S; y

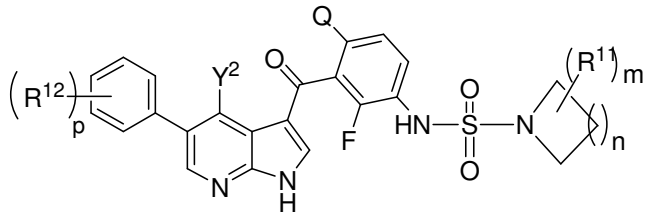
el subíndice p es un número entero de 1 a 5.

8. El compuesto de la Reivindicación **8,** que tiene formula (Id-1):



. Id-1

9. El compuesto de la Reivindicación **8**, que tiene formula (Id-2):



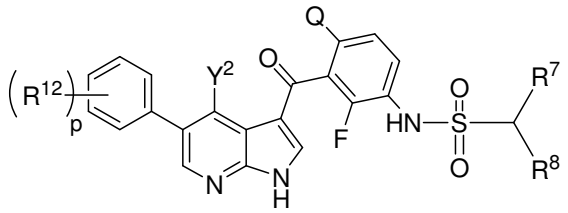
Id-2

donde R^{11} es C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo, heterocicloalquilo, heterocicloalquiloalquilo o R^e;

el subíndice m es un número entero de 0 a 3; y

el subíndice n es un número entero de 1 a 5.

10. El compuesto de la Reivindicación **8**, que tiene formula (Id-3):

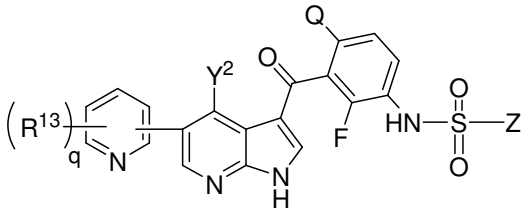


Id-3

donde R^7 y R^8 son cada uno por separado C_{1-6}alquilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo o $-X^2R^9$, donde la porción alifática o aromática de R^7 y R^8 es cada una sustituida opcionalmente con 1 a 3 miembros seleccionados por separado del grupo que consiste en C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo y R^e, proporcionado en cada aparición, como mínimo dos opciones cualesquiera de los grupos R^6, R^7

y R^8 grupos no son simultáneamente hidrógeno; y donde X^2 es $-NR^{10}$, O o S; R^{10} es H, C_{1-6}alquilo o arilo; y R^9 es H, C_{1-6}alquilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo o heteroariloalquilo, donde R^9 es sustituido opcionalmente con 1 a 3 sustituyentes R^e.

11. El compuesto de la Reivindicación **1**, que tiene formula (Ie):



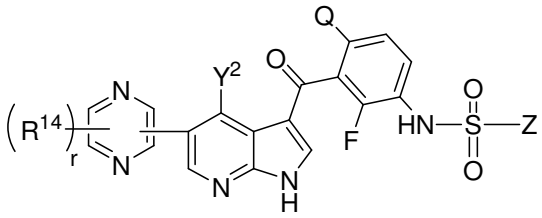
Ie

donde

R^{13} es H o R^1; o dos grupos adyacentes R^{13} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S; y

el subíndice q es un número entero de 1 a 4.

12. El compuesto de la Reivindicación **1**, que tiene formula (If):



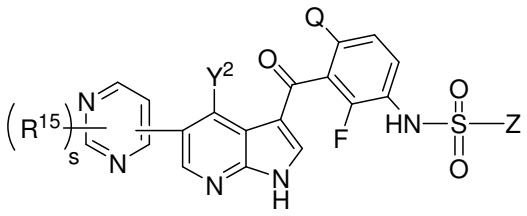
If

donde

R^{14} es H o R^1; o dos grupos adyacentes R^{14} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S; y

el subíndice r es un número entero de 1 a 3.

13. El compuesto de la Reivindicación **1,** que tiene formula (Ig):



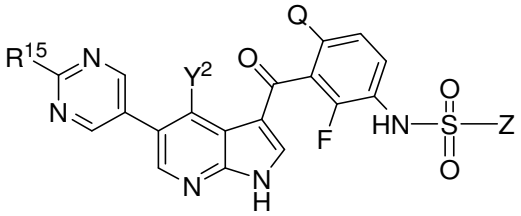
Ig

donde

R^{15} es H o R^1; o dos grupos adyacentes R^{15} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S; y

el subíndice s es un número entero de 1 a 3.

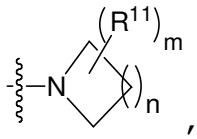
14. El compuesto de la Reivindicación **14,** que tiene formula (Ig-1):



Ig-1

15. El compuesto de la Reivindicación **14** o 1**5,** donde Z es $-N(R^4)(R^5)$.

16. El compuesto de la Reivindicación **14** o 1**5**, donde Z es:



donde R^{11} es C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo o R^e;

el subíndice m es un número entero de 0 a 3;

el subíndice n es un número entero de 1 a 5; y la línea ondulada indica el punto de unión al grupo SO_2 de las fórmulas Ig o Ig-1.

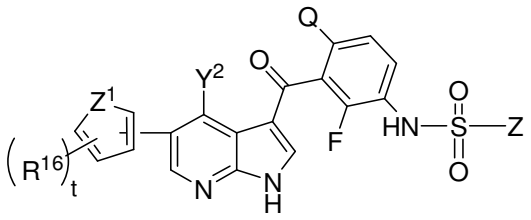
17. El compuesto de la Reivindicación **14** o 1**5**, donde:

Z es $-CH(R^7)(R^8)$; y

R^7 y R^8 son cada uno por separado C_{1-6}alquilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo o $-X^2R^9$, donde la porción alifática o aromática de R^7 y R^8 es cada una sustituida opcionalmente con 1 a 3 miembros seleccionados por separado del grupo que consiste en C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo y R^e, proporcionado en cada aparición, como mínimo dos opciones cualesquiera de los grupos R^6, R^7 y R^8 grupos no son simultáneamente hidrógeno; y donde X^2 es $-NR^{10}$, O o S; R^{10} es H, C_{1-6}alquilo o arilo; y R^9 es H, C_{1-6}alquilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-}

$_8$cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo o heteroariloalquilo, donde R^9 es sustituido opcionalmente con 1 a 3 R^e sustituyentes.

18. El compuesto de la Reivindicación **1,** que tiene formula (Ih):



Ih

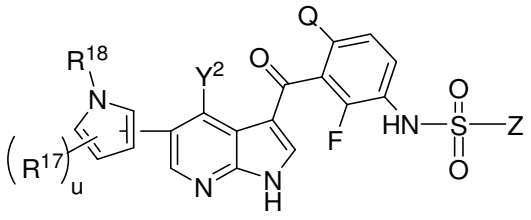
donde

Z^1 es O o S;

R^{16} es H o R^1; o dos grupos adyacentes R^{16} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S; y

el subíndice t es un número entero de 1 a 3.

19. El compuesto de la Reivindicación **1,** que tiene formula (Ii):



Ii

donde

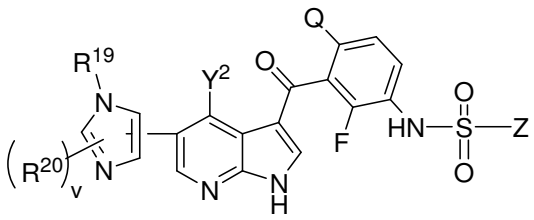
R^{17} es H o R^1; o dos grupos adyacentes R^{17} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo selec-

cionados de O, N o S; o R^{17} y R^{18} tomados junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S;

R^{18} es H, C_{1-6}alquilo, C_{1-6}haloalquilo, C_{3-6}cicloalquilo o C_{3-6}cicloalquilo; y

el subíndice u es un número entero de 1 a 3.

20. El compuesto de la Reivindicación **1,** que tiene formula (Ij):



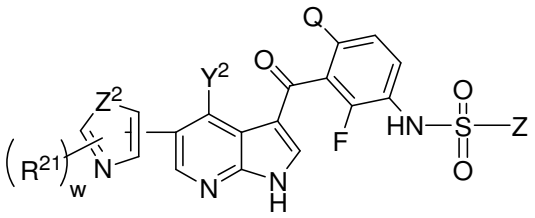
Ij

R^{20} es H o R^{1}; o dos grupos adyacentes R^{20} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S; o R^{20} y R^{19} tomados junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S;

R^{19} es H, C_{1-6}alquilo, C_{1-6}haloalquilo, C_{3-6}cicloalquilo o C_{3-6}cicloalquilo; y

el subíndice v es un número entero de 1 o 2.

21. El compuesto de la Reivindicación **1,** que tiene formula (Ik):



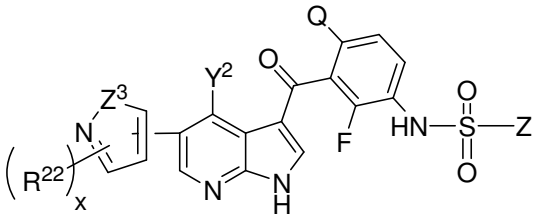
Ik

R^{21} es H o R^1; o dos grupos adyacentes R^{21} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S;

Z^2 es O o S; y

el subíndice w es un número entero de 1 o 2.

22. El compuesto de la Reivindicación **1,** que tiene formula (Il):



Il

R^{22} es H o R^1; o dos grupos adyacentes R^{22} junto con los átomos a los cuales están unidos forman un anillo de 5 a 6 miembros que tiene 0-2 heteroátomos como miembros de anillo seleccionados de O, N o S;

Z^3 es O, S o-N(R^{30}), donde R^{30} es H, C_{1-6}alquilo, C_{1-6}haloalquilo, C_{3-6}cicloalquilo o C_{3-6}cicloalquilo; y

el subíndice x es un número entero de 1 o 2.

23. El compuesto de cualquiera de las reivindicaciones **1-7,** donde Y^1 se selecciona del grupo que consiste en fenilo y naftilo, cada uno de los cuales es sustituido opcionalmente

por separado con 1–3 grupos R^1, donde la porción aromática de R^1 es sustituido opcionalmente con 1–3 sustituyentes seleccionados por separado de R^e; o dos grupos adyacentes R^1 en el anillo de fenilo o naftilo junto con los átomos a los cuales están unidos forman un anillo de 5 o 6 miembros que tiene de 0 a 2 heteroátomos adicionales seleccionados de N, O o S, sustituido opcionalmente con 1 a 3 sustituyentes R^d.

24. El compuesto de cualquiera de las reivindicaciones **1**–**7**, donde Y^1 es heteroarilo de 5 o 6 miembros, cada uno de los cuales se sustituye opcionalmente por separado con 1–3 grupos R^1, donde la porción aromática de R^1 es sustituida opcionalmente con 1–3 sustituyentes seleccionados por separado de R^e; o dos grupos adyacentes R^1 en el anillo de fenilo o naftilo junto con los átomos a los cuales están unidos forman un anillo de 5 o 6 miembros que tiene de 0 a 2 heteroátomos adicionales seleccionados de N, O o S, sustituido opcionalmente con 1 a 3 sustituyentes R^d.

25. El compuesto de la Reivindicación **24** o 2**5**, donde cada R^1 es seleccionado por separado de halógeno, –CN, –OH, $-CF_3$, CF_3O–, C_{1-6}alquilo, C_{1-6}alcoxi, C_{3-6}cicloalcoxi, $-NO_2$, bencilo, fenilo, ciclopropilo, ciclopropilometilo, 1-cicanociclopropilo, 1-carboxiciclopropilo, 1-carbamoilociclopropilo, 1-metoxicarbonilociclopropilo, 1-cianoisopropilo, 1-hidroxiciclopropilo, 1-hidroxiisopropilo, ciclobutoxi, ciclopentoxi, cicloheiloxi, C_{1-6}alquilo-1,2,4-oxadiazol-3-il, 5-C_{1-}

$_6$alquilo-1,3,4-oxadiazol-2il, 5-di(C_{1-6}alquilo)amino-1,3,4-oxadiazol-2il, 5-C_{1-6}alquiloamino-1,3,4-tiadiazol-2-il, ciclobutilo, ciclobutilometilo, ciclopentilo, ciclopentilometilo, ciclohexilo, cicloheximetilo, $-OC(O)R^b$, $-C(O)R^b$, $-C(O)OR^b$, $-NHC(O)R^b$, $-C(O)NHR^b$, $-NHR^b$ o $-NR^bR^b$.

26. El compuesto de la Reivindicación **26**, donde R^1 es F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, C_2H_5O-, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, 1-carboxiciclopropilo, 1-carbamoilociclopropilo, 1-metoxicarbonilociclopropilo, 1-cianoisopropilo, 1-hidroxiciclopropilo, 1-hidroxiisopropilo, ciclobutoxi, ciclopentoxi, cicloheiloxi, 4-morfolino, 4-hidroxipiperidinilo,1- piperidinilo, piperacinilo, 4-metilpiperacinilo, 4-t-butoxicarbonilopiperacinilo, azetidinilo, pirrolidinilo, ciclopropilocarbamoilo, 5-metil-1,2,4-oxadiazol-3-il, 5-metil-1,3,4-oxadiazol-2il, 5-dimetilamino-1,3,4-oxadiazol-2il, 5-metilamino-1,3,4-tiadiazol-2-il, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, isopropilo, 1-pirrolidinilo, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo.

27. El compuesto de cualquiera de las reivindicaciones **1** y **3**-**7**, donde Y^1 es CN, halógeno, -OH, CH_3, CH_3O-, CF_3, CF_3O, ciclopropilo o ciclopropilometilo.

28. El compuesto de cualquiera de las reivindicaciones **1–7**, donde (i) Y^1 se selecciona del grupo que consiste en 5-pirimidinilo, 2-pirimidinilo, 4-pirimidinilo, 2-metoxi-5-pirimidinilo, 2-metoxi-3-pirimidinilo, 2-metoxi-4-pirimidinilo, 4-metoxi-2-pirimidinilo, 4-metoxi-4-pirimidinilo, 4-metoxi-5-pirimidinilo, 5-metoxi-2-pirimidinilo, 5-metoxi-4-pirimidinilo, 2-ciclopropilo-5-pirimidinilo, 2-ciclopropilo-3-pirimidinilo, 2-ciclopropilo-4-pirimidinilo, 4-ciclopropilo-2-pirimidinilo, 4-ciclopropilo-4-pirimidinilo, 4-ciclopropilo-5-pirimidinilo, 5-ciclopropilo-2-pirimidinilo, 5-ciclopropilo-4-pirimidinilo, 2-ciclopropilometilo-5-pirimidinilo, 2-ciclopropilometilo-3-pirimidinilo, 2-ciclopropilometilo-4-pirimidinilo, 4-ciclopropilometilo-2-pirimidinilo, 4-ciclopropilometilo-4-pirimidinilo, 4-ciclopropilometilo-5-pirimidinilo, 5-ciclopropilometilo-2-pirimidinilo, 5-ciclopropilometilo-4-pirimidinilo, 2-metil-5-pirimidinilo, 2-metil-3-pirimidinilo, 2-metil-4-pirimidinilo, 4-metil-2-pirimidinilo, 4-metil-4-pirimidinilo, 4-metil-5-pirimidinilo, 5-metil-2-pirimidinilo, 5-metil-4-pirimidinilo, 2-halo-5-pirimidinilo, 2-halo-3-pirimidinilo, 2-halo-4-pirimidinilo, 4-halo-2-pirimidinilo, 4-halo-4-pirimidinilo, 4-halo-5-pirimidinilo, 5-halo-2-pirimidinilo, 5-halo-4-pirimidinilo, 2-(1-cianociclopropilo)-5-pirimidinilo, 2-(1-cianociclopropilo)-3-pirimidinilo, 2-(1-cianociclopropilo)-4-pirimidinilo, 4-(1-cianociclopropilo)-2-pirimidinilo, 4-(1-cianociclopropilo)-4-pirimidinilo, 4-(1-

cianociclopropilo)-5-pirimidinilo, 5-(1-cianociclopropilo)-2-pirimidinilo, 5-(1-cianociclopropilo)-4-pirimidinilo, 2-ciclopropiloamino-5-pirimidinilo, 2-ciclopropiloamino-3-pirimidinilo, 2-ciclopropiloamino-4-pirimidinilo, 4-ciclopropiloamino-2-pirimidinilo, 4-ciclopropiloamino-4-pirimidinilo, 4-ciclopropiloamino-5-pirimidinilo, 5-ciclopropiloamino-2-pirimidinilo, 5-ciclopropiloamino-4-pirimidinilo, 2-dimetilamino-5-pirimidinilo, 2-dimetilamino-3-pirimidinilo, 2-dimetilamino-4-pirimidinilo, 4-dimetilamino-2-pirimidinilo, 4-dimetilamino-4-pirimidinilo, 4-dimetilamino-5-pirimidinilo, 5-dimetilamino-2-pirimidinilo, 5-dimetilamino-4-pirimidinilo, 2-ciano-5-pirimidinilo, 2-ciano-3-pirimidinilo, 2-ciano-4-pirimidinilo, 4-ciano-2-pirimidinilo, 4-ciano-4-pirimidinilo, 4-ciano-5-pirimidinilo, 5-ciano-2-pirimidinilo, 5-ciano-4-pirimidinilo, 2-trifluorometil-5-pirimidinilo, 2-trifluorometil-3-pirimidinilo, 2-trifluorometil-4-pirimidinilo, 4-trifluorometil-2-pirimidinilo, 4-trifluorometil-4-pirimidinilo, 4-trifluorometil-5-pirimidinilo, 5-trifluorometil-2-pirimidinilo, 5-trifluorometil-4-pirimidinilo, 2-trifluorometoxi-5-pirimidinilo, 2-trifluorometoxi-3-pirimidinilo, 2-trifluorometoxi-4-pirimidinilo, 4-trifluorometoxi-2-pirimidinilo, 4-trifluorometoxi-4-pirimidinilo, 4-trifluorometoxi-5-pirimidinilo, 5-trifluorometoxi-2-pirimidinilo, 5-trifluorometoxi-4-pirimidinilo, 2-hidroxi-5-pirimidinilo, 2-hidroxi-3-

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piridilo, 5-ciano-3-piridilo, 6-ciano-3-piridilo, 2-ciano-4-piridilo, 3-ciano-4-piridilo, 3-hidroxi-2-piridilo, 4-hidroxi-2-piridilo, 5-hidroxi-2-piridilo, 6-hidroxi-2-piridilo, 2-hidroxi-3-piridilo, 4-hidroxi-3-piridilo, 5-hidroxi-3-piridilo, 6-hidroxi-3-piridilo, 2-hidroxi-4-piridilo, 3-hidroxi-4-piridilo, 3-trifluorometil-2-piridilo, 4-trifluorometil-2-piridilo, 5-trifluorometil-2-piridilo, 6-trifluorometil-2-piridilo, 2-trifluorometil-3-piridilo, 4-trifluorometil-3-piridilo, 5-trifluorometil-3-piridilo, 6-trifluorometil-3-piridilo, 2-trifluorometil-4-piridilo, 3-trifluorometil-4-piridilo, 3-amino-2-piridilo, 4-amino-2-piridilo, 5-amino-2-piridilo, 6-amino-2-piridilo, 2-amino-3-piridilo, 4-amino-3-piridilo, 5-amino-3-piridilo, 6-amino-3-piridilo, 2-amino-4-piridilo, 3-amino-4-piridilo, 3-trifluorometoxi-2-piridilo, 4-trifluorometoxi-2-piridilo, 5-trifluorometoxi-2-piridilo, 6-trifluorometoxi-2-piridilo, 2-trifluorometoxi-3-piridilo, 4-trifluorometoxi-3-piridilo, 5-trifluorometoxi-3-piridilo, 6-trifluorometoxi-3-piridilo, 2-trifluorometoxi-4-piridilo, 3-trifluorometoxi-4-piridilo, 3-metil-2-piridilo, 4-metil-2-piridilo, 5-metil-2-piridilo, 6-metil-2-piridilo, 2-metil-3-piridilo, 4-metil-3-piridilo, 5-metil-3-piridilo, 6-metil-3-piridilo, 2-metil-4-piridilo, 3-metil-4-piridilo, 3-metoxi-2-piridilo, 4-metoxi-2-piridilo, 5-metoxi-2-piridilo, 6-metoxi-2-piridilo, 2-metoxi-3-piridilo, 4-metoxi-3-piridilo, 5-metoxi-3-piridilo, 6-metoxi-3-piridilo, 2-metoxi-4-piridilo, 3-metoxi-4-piridilo, 3-

ciclopropilo-2-piridilo, 4-ciclopropilo-2-piridilo, 5-ciclopropilo-2-piridilo, 6-ciclopropilo-2-piridilo, 2-ciclopropilo-3-piridilo, 4-ciclopropilo-3-piridilo, 5-ciclopropilo-3-piridilo, 6-ciclopropilo-3-piridilo, 2-ciclopropilo-4-piridilo, 3-ciclopropilo-4-piridilo, 3-ciclopropilometilo-2-piridilo, 4-ciclopropilometilo-2-piridilo, 5-ciclopropilometilo-2-piridilo, 6-ciclopropilometilo-2-piridilo, 2-ciclopropilometilo-3-piridilo, 4-ciclopropilometilo-3-piridilo, 5-ciclopropilometilo-3-piridilo, 6-ciclopropilometilo-3-piridilo, 2-ciclopropilometilo-4-piridilo, 3-ciclopropilometilo-4-piridilo, 3-ciclopropiloamino-2-piridilo, 4-ciclopropiloamino-2-piridilo, 5-ciclopropiloamino2-piridilo, 6-ciclopropiloamino-2-piridilo, 2-ciclopropiloamino-3-piridilo, 4-ciclopropiloamino-3-piridilo, 5-ciclopropiloamino-3-piridilo, 6-ciclopropiloamino-3-piridilo, 2-ciclopropiloamino-4-piridilo, 3-ciclopropiloamino-4-piridilo, 3-ciclopropilometiloamino-2-piridilo, 4-ciclopropilometiloamino-2-piridilo, 5-ciclopropilometiloamino-2-piridilo, 6-ciclopropilometiloamino-2-piridilo, 2-ciclopropilometiloamino-3-piridilo, 4-ciclopropilometiloamino-3-piridilo, 5-ciclopropilometiloamino-3-piridilo, 6-ciclopropilometiloamino-3-piridilo, 2-ciclopropilometiloamino-4-piridilo, 3-ciclopropilometiloamino-4-piridilo, 3-metilamino-2-piridilo, 4-metilamino-2-piridilo, 5-metilamino-2-piridilo, 6-metilamino-2-piridilo, 2-metilamino-3-piridilo, 4-metilamino-3-piridilo, 5-metilamino-3-piridilo, 6-

metilamino-3-piridilo, 2-metilamino-4-piridilo, 3-metilamino-4-piridilo, 3-dimetilamino-2-piridilo, 4-dimetilamino-2-piridilo, 5-dimetilamino-2-piridilo, 6-dimetilamino-2-piridilo, 2-dimetilamino-3-piridilo, 4-dimetilamino-3-piridilo, 5-dimetilamino-3-piridilo, 6-dimetilamino-3-piridilo, 2-dimetilamino-4-piridilo, 3-dimetilamino-4-piridilo, 3-metiltio-2-piridilo, 4-metiltio-2-piridilo, 5-metiltio-2-piridilo, 6-metiltio-2-piridilo, 2-metiltio-3-piridilo, 4-metiltio-3-piridilo, 5-metiltio-3-piridilo, 6-metiltio-3-piridilo, 2-metiltio-4-piridilo, 3-metiltio-4-piridilo, 3-acetoxi-2-piridilo, 4-acetoxi-2-piridilo, 5-acetoxi-2-piridilo, 6-acetoxi-2-piridilo, 2-acetoxi-piridilo, 4-acetoxi-3-piridilo, 5-acetoxi-3-piridilo, 6-acetoxi-3-piridilo, 2-acetoxi-4-piridilo, 3-acetoxi-4-piridilo, 3-acetilo-2-piridilo, 4-acetilo-2-piridilo, 5-acetilo-2-piridilo, 6-acetilo-2-piridilo, 2-acetilo-piridilo, 4-acetilo-3-piridilo, 5-acetilo-3-piridilo, 6-acetilo-3-piridilo, 2-acetilo-4-piridilo, 3-acetilo-4-piridilo, 3-metoxicarbonilo-2-piridilo, 4-metoxicarbonilo-2-piridilo, 5-metoxicarbonilo-2-piridilo, 6-metoxicarbonilo-2-piridilo, 2-metoxicarbonilo-3-piridilo, 4-metoxicarbonilo-3-piridilo, 5-metoxicarbonilo-3-piridilo, 6-metoxicarbonilo-3-piridilo, 2-metoxicarbonilo-4-piridilo, 3-metoxicarbonilo-4-piridilo, 3-metilcarbamoilo-2-piridilo, 4-metilcarbamoilo-2-piridilo, 5-metilcarbamoilo-2-piridilo, 6-metilcarbamoilo-2-piridilo, 2-metilcarbamoilo-3-piridilo, 4-metilcarbamoilo-3-piridilo, 5-

metilcarbamoilo-3-piridilo, 6-metilcarbamoilo-3-piridilo, 2-metilcarbamoilo-4-piridilo, 3-metilcarbamoilo-4-piridilo, 3-acetamido-2-piridilo, 4-acetamido-2-piridilo, 5-acetamido-2-piridilo, 6-acetamido-2-piridilo, 2-acetamido-3-piridilo, 4-acetamido-3-piridilo, 5-acetamido-3-piridilo, 6-acetamido-3-piridilo, 2-acetamido-4-piridilo y 3-acetamido-4-piridilo, 3-(1-cianociclopropilo)-2-piridilo, 4-(1-cianociclopropilo)-2-piridilo, 5-(1-cianociclopropilo)-2-piridilo, 6-(1-cianociclopropilo)-2-piridilo, 2-(1-cianociclopropilo)-3-piridilo, 4-(1-cianociclopropilo)-3-piridilo, 5-(1-cianociclopropilo)-3-piridilo, 6-(1-cianociclopropilo)-3-piridilo y 2-(1-cianociclopropilo)-4-piridilo, 3-(1-cianociclopropilo)-4-piridilo, cada uno de los cuales es sustituido opcionalmente con 1 a 2 sustituyentes seleccionados por separado de F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, 1-cianociclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido o metilcarbamoilo; o (ii)Y^1 se selecciona del grupo que consiste en 4-pirimidinilo, 5-pirimidinilo, 2-piracinilo, 2-tiazolilo, 4-tiazolilo, 5-tiazolilo, 2- tiofenilo, 3-tiofenilo, 2-amino-quinazolin-5-il, 2-amino-quinazolin-6-il, 2-amino-quinazolin-6-il, 2-amino-quinazolin-7-il, 2-amino-quinazolin-8-il, 2-oxo-6-indolinilo, 2-oxo-4-indolinilo, 2-oxo-5-indolinilo, 2-oxo-7-indolinilo, 2-piridilo, 3-piridilo, 4-piridilo, 1H-indazol-4-il,

1H-indazol-5-il, 1H-indazol-6-il y 1H-indazol-7-il, cada uno de los cuales es sustituido con 1 a 2 sustituyentes seleccionados por separado de F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, C_2H_5O-, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, 1-carboxiciclopropilo, 1-carbamoilociclopropilo, 1-metoxicarbonilociclopropilo, 1-cianoisopropilo, 1-hidroxiciclopropilo, 1-hidroxiisopropilo, ciclobutoxi, ciclopentoxi, cicloheiloxi, 4-morfolino, 4-hidroxipiperidinilo,1- piperidinilo, piperacinilo, 4-metilpiperacinilo, 4-t-butoxicarbonilopiperacinilo, azetidinilo, pirrolidinilo, ciclopropilocarbamoilo, 5-metil-1,2,4-oxadiazol-3-il, 5-metil-1,3,4-oxadiazol-2il, 5-dimetilamino-1,3,4-oxadiazol-2il, 5-metilamino-1,3,4-tiadiazol-2-il, metilamino metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, isopropilo, 1-pirrolidinilo, 1-ciclopropiloetilo, 2-ciclopropiloetilo, 1-ciclopropiloetilamino, 2-ciclopropiloetilamino o 1-hidroxi-1-metiletilo.

29. El compuesto de cualquiera de las reivindicaciones **1-7**, donde (i) Y^1 se selecciona del grupo que consiste en fenilo, 2-halofenilo, 3-halofenilo, 4-halofenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-cianofenilo, 3-cianofenilo, 4-cianofenilo, 2-hidroxifenilo, 3-hidroxifenilo, 4-hidroxifenilo, 2-trifluorometilfenilo, 3-trifluorometilfenilo, 4-trifluorometilfenilo, 2-aminofenilo, 3-aminofenilo, 4-

aminofenilo, 2-trifluorometilfenilo, 3-trifluorometilfenilo, 4-trifluorometilfenilo, 2-metilfenilo, 3-metilfenilo, 4-metilfenilo, 2-metoxifenilo, 3-metoxifenilo, 4-metoxifenilo, 2-ciclopropilofenilo, 3-ciclopropilofenilo, 4-ciclopropilofenilo, 2-ciclopropilometilofenilo, 3- ciclopropilometilofenilo, 4-ciclopropilometilofenilo, 2-ciclopropilometiloaminofenilo, 3-ciclopropilometiloaminofenilo, 4-ciclopropilometiloaminofenilo, 2-ciclopropiloaminofenilo, 3-ciclopropiloaminofenilo, 4-ciclopropiloaminofenilo, 2-metilaminofenilo, 3-metilaminofenilo, 4-metilaminofenilo, 2-dimetilaminofenilo, 3-dimetilaminofenilo, 4-dimetilaminofenilo, 2-metiltiofenilo, 3-metiltiofenilo, 4-metiltiofenilo, 2-acetoxifenilo, 3-acetoxifenilo, 4-acetoxifenilo, 2-acetilofenilo, 3-acetilofenilo, 4-acetilofenilo, 2-metoxicarbonilofenilo, 3-metoxicarbonilofenilo, 4-metoxicarbonilofenilo, 2-acetamidofenilo, 3-acetamidofenilo, 4-acetamidofenilo, 2-metilcarbamoilofenilo, 3-metilcarbamoilofenilo, 4-metilcarbamoilofenilo, 2-(1-cianociclopropilo)fenilo, 3-(1-cianociclopropilo)fenilo y 4-(1-cianociclopropilo)fenilo, cada uno de los cuales es sustituido opcionalmente con 1 a 2 sustituyentes seleccionados por separado de F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, 1-cianociclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido o metilcarbamoilo; o (ii) Y^1 es fenilo sustituido con 1 a 2 sustituyentes

seleccionados por separado de F, Cl, Br, I, –CN, –OH, $–CF_3$, NH_2, $CF_3O–$, $CH_3–$, CH_3O, $C_2H_5O–$, $–NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1–cianociclopropilo, 1–carboxiciclopropilo, 1–carbamoilociclopropilo, 1–metoxicarbonilociclopropilo, 1–cianoisopropilo, 1–hidroxiciclopropilo, 1–hidroxiisopropilo, ciclobutoxi, ciclopentoxi, cicloheiloxi, 4–morfolino, 4–hidroxipiperidinilo, 1–piperidinilo, 1–piperacinilo, 4–metilpiperacinilo, 4–t–butoxicarbonilopiperacinilo, azetidinilo, pirrolidinilo, ciclopropilocarbamoilo, 5–metil–1,2,4–oxadiazol–3–il, 5–metil–1,3,4–oxadiazol–2il, 5–dimetilamino–1,3,4–oxadiazol–2il, 5–metilamino–1,3,4–tiadiazol–2–il, metilamino metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, isopropilo, 1–pirrolidinilo, 1–ciclopropiloetilo, 2–ciclopropiloetilo, 1–ciclopropiloetilamino, 2–ciclopropiloetilamino o 1–hidroxi–1–metiletilo.

30. El compuesto de cualquiera de las reivindicaciones **1–23**, donde Y^2 es H, halógeno, CN, C_{1-6}alquilo, C_{1-6}alcoxi, C_{3-6}cicloalquiloamino, C_{3-6}cicloalquilo–C_{1-3}alquiloamino, arilo, heteroarilo, ariloalquilo o heteroariloalquilo.

31. El compuesto de la Reivindicación **30**, donde Y^2 es H, F, Cl, I, CN, CH_3, $CH_3O–$, ciclopropiloamino o ciclopropilometiloamino.

32. El compuesto de cualquiera de las reivindicaciones **1–5**, **8–9**, **12–16** y **19–23**, donde R^4 y R^5 son seleccionados cada

uno por separado de C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, arilo-C_{1-4}alquilo, heteroarilo o heteroarilo-C_{1-4}alquilo, cada uno de los cuales es sustituido opcionalmente con 1-3 sustituyentes seleccionados por separado de C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo o R^e.

33. El compuesto de cualquiera de las reivindicaciones **1-5**, **8-9**, **12-16** y **19-23**, donde R^4 es $-CH_3$ y R^5 es C_{2-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, arilo-C_{1-4}alquilo, heteroarilo o heteroarilo-C_{1-4}alquilo, cada uno de los cuales es sustituido opcionalmente con 1-3 sustituyentes seleccionados por separado de C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo o R^e.

34. El compuesto de la Reivindicación **33**, donde R^4 y R^5 son seleccionados cada uno por separado de CH_3, etilo, propilo, butilo, pentilo, ciclopropilo, ciclopropilometilo, ciclobutilo, ciclobutilometilo, ciclopentilo, ciclopentilometilo, ciclohexilo, ciclohexilometilo, fenilo o bencilo, cada uno de los cuales es sustituido opcionalmente con 1-3 sustituyentes seleccionados por separado de F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo,

acetamido, metilcarbamoilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-piridilometilo, 3-piridilometilo, 4-piridilometilo, 2-oxetanilo, 3-oxtetanilo, 2-oxetanilometilo, 3-oxtetanilometilo, 2-tetrahidrofuranilo, 3-tetrahidrofuranilo, 2-tetrahidrofuranilometilo, 3-tetrahidrofuranilometilo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-tetrahidrotiofenilo, 3-tetrahidrotiofenilo, 4-morfolinilo, 2-morfolinilo o 3-morfolinilo.

35. El compuesto de la Reivindicación **33**, donde R^4 es CH_3 y R^5 es seleccionado de etilo, propilo, butilo, pentilo, ciclopropilo, ciclopropilometilo, ciclobutilo, ciclobutilometilo, ciclopentilo, ciclopentilometilo, ciclohexilo, ciclohexilometilo, fenilo o bencilo, cada uno de los cuales es sustituido opcionalmente con 1–3 sustituyentes seleccionados por separado de F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1–cianociclopropilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido, metilcarbamoilo, 2–piridilo, 3–piridilo, 4–piridilo, 2–piridilometilo, 3–piridilometilo, 4–piridilometilo, 2–oxetanilo, 3–oxtetanilo, 2–oxetanilometilo, 3–oxtetanilometilo, 2–tetrahidrofuranilo, 3–tetrahidrofuranilo, 2–tetrahidrofuranilometilo, 3–tetrahidrofuranilometilo, 1–pirrolidinilo, 2–pirrolidinilo, 3–pirrolidinilo, 2–tetrahidrotiofenilo, 3–tetrahidrotiofenilo, 4–morfolinilo, 2–morfolinilo o 3– morfolinilo.

36. El compuesto de cualquiera de las reivindicaciones **1**–**4**, **8**–**9**, **12**–**16** y **19**–**23**, donde Z se selecciona del grupo que consiste en ciclopropilo, ciclobutilo, ciclohexilo, ciclopentilo, cicloheptilo, ciclooctilo, 1–azetindinilo, 1–pirrolidinilo, 1–piperidinilo, 4–morfolinilo, 4–tiomorfolinilo 3–oxazolidinilo, 3–tiazolidinilo, 2–isoxazolidinilo, 2–isotiazolidinilo, 1–pirazolidinilo, 1–piperacinilo, 1–hexahidropirimidinilo y 1–

hexahidropiridacinilo, cada uno de los cuales es sustituido opcionalmente con uno a tres R^{24} sustituyentes seleccionados por separado del grupo que consiste en halógeno, C_{1-6}alquilo, C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{1-6}alquilo, C_{3-8}cicloalquilo, C_{3-8}cicloalquiloalquilo, heterocicloalquilo, heterocicloalquiloalquilo, arilo, ariloalquilo, heteroarilo, heteroariloalquilo y R^c; o dos grupos sustituyentes R^{24} adyacentes junto con el átomo al cual están unidos forman un anillo aromático de 5 o 6 miembros que tiene de 0 a 2 átomos adicionales como miembros de anillo seleccionados de O, N o S.

37. El compuesto de cualquiera de las reivindicaciones **1**–**4**, **8**–**9**, **12**–**16** y **19**–**23**, donde Z se selecciona del grupo que consiste en 1-pirrolidinilo, sec-butilo, pentan-2-il, pentan-3-il, ciclopropilo, $(CH_3)(CF_3CH_2)N$-, ciclopropilometiloamino, ciclobutilo y Ciclopentilo, cada uno de los cuales es sustituido opcionalmente con 1-2 miembros seleccionados de -F, metoxicarbonilo, etoxicarbonilo, $-CH_3$, $CH_3(CO)NH$-, vinilo, propen-3-ilo o $CH_3(CO)(CH_3)N$-.

38. El compuesto de cualquiera de las reivindicaciones **6**, **10** y **17**, donde n es 1, 2, 3 o 4.

39. El compuesto de cualquiera de las reivindicaciones **6**, **10** y **17**, donde el subíndice m es 0.

40. El compuesto de cualquiera de las reivindicaciones **6**, **10** y **17**, donde R^{11} es H, F, Cl, Br, I, -CN, -OH, $-CF_3$, NH_2,

CF_3O–, CH_3–, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, fenilo, bencilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, etioxicarbonilo, acetamido, metilcarbamoilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-piridilometilo, 3-piridilometilo, 4-piridilometilo, 2-oxetanilo, 3-oxtetanilo, 2-oxetanilometilo, 3-oxtetanilometilo, 2-tetrahidrofuranilo, 3-tetrahidrofuranilo, 2-tetrahidrofuranilometilo, 3-tetrahidrofuranilometilo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-tetrahidrotiofenilo, 3-tetrahidrotiofenilo, 4-morfolinilo, 2-morfolinilo, 3- morfolinilo, 1-pirrolidinilo, 2-pirrolidinilo, 1-pirazolilo, 3-pirazolilo, 4-pirazolilo, 5-pirazolilo, 2-tiofenilo, 3-tiofenilo, 1-imidazolilo, 2-imidazolilo, 4-imidazolilo¸ 5-imidazolilo o 2-tiazolilo.

41. El compuesto de cualquiera de las reivindicaciones **9**–**23**, donde R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} y R^{22} son seleccionados cada uno por separado de H, CN, halógeno, –OH, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, C_{3-8}cicloalquilo, C_{3-8}cicloalquilo–C_{1-4}alquilo, arilo, ariloalquilo, heterocicloalquilo, heterocicloalquilo–C_{1-4}alquilo, heteroarilo y heterocicloalquilo, donde la porción alifática o aromática de R^{12} es sustituido opcionalmente además con 1–3 sustituyentes seleccionados de F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O–, CH_3–, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclo-

propilometiloamino, 1-cianociclopropilo, bencilo, benciloxi, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido o metilcarbamoilo.

42. El compuesto de la Reivindicación **42**, donde R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} y R^{22} son seleccionados cada uno por separado de H, F, Cl, Br, I, –CN, –OH, $-CF_3$, NH_2, CF_3O-, CH_3-, CH_3O, $-NO_2$, ciclopropilo, ciclopropilometilo, ciclopropiloamino, ciclopropilometiloamino, 1-cianociclopropilo, bencilo, metilamino, dimetilamino, metiltio, acetoxi, acetilo, metoxicarbonilo, acetamido o metilcarbamoilo.

43. Un compuesto seleccionados de cualquiera de compuestos P-0012 a P-0117 y P-0223 a P-0351 según se establece en Tabla 2 o sales, hidratos, solvatos, tautómeros e isómeros de los mismos aceptables farmacéuticamente.

44. Un compuesto seleccionado de cualquiera de los compuestos P-0118 a P-0222 según se establece en la Tabla 3 o sales, hidratos, solvatos, tautómeros e isómeros de los mismos aceptables farmacéuticamente.

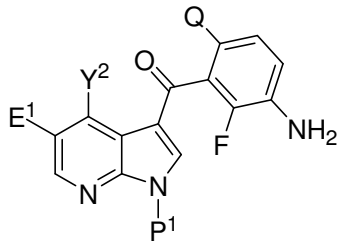
45. Una composición que comprende un compuesto de cualquiera de las reivindicaciones **1**–**45** y un excipiente o soporte aceptable farmacéuticamente.

46. Una composición que comprende un compuesto de cualquiera de las reivindicaciones **1–45** y otro agente terapéutico.

47. Un equipo que comprende un compuesto de cualquiera de las reivindicaciones **1–45.**

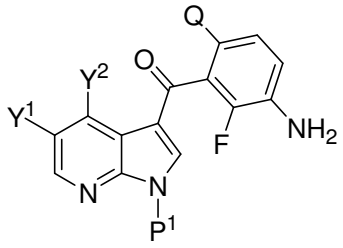
48. Un método para preparar un compuesto de fórmula (I) de conformidad con la Reivindicación **1,** dicho método comprende:

poner en contacto un compuesto que tiene formula II:

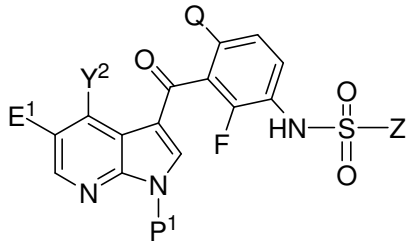


II

con un agente de fórmula (III): $Y^1–G^1$ o formula (IV): $A^1–S(O)_2–Z$ (IV) en condiciones suficientes para producir un compuesto que tiene formulas (V) o (VI):



o



(V) (VI)

Reacción de (i) un compuesto de fórmula (V) con un compuesto de fórmula (IV), o (ii) un compuesto de fórmula (VI) con un agente de fórmula (III) en condiciones suficientes para producir el compuesto de fórmula (I); donde dicho contacto o reacción con el agente de fórmula (III) se hace en presencia de un complejo de paladio; y donde

E^1 es halógeno, tosilato o mesilato;

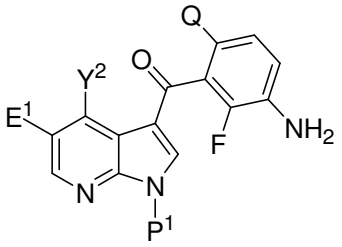
G^1 es $-B(OR^{25})_2$ o $-Sn(Bu)_3$, donde R^{25} es –OH, alquilo o dos $-OR^{25}$ sustituyentes junto con el átomo de boro a los cuales están unidos para formar un anillo de 5 o 6 miembros sustituido opcionalmente;

A^1 es un grupo saliente; y

P^1 es H o un grupo protector amino.

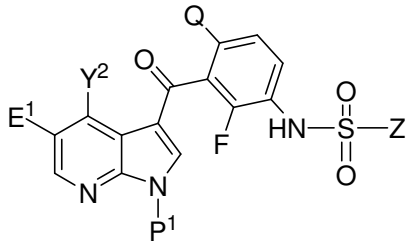
49. Un método para preparar un compuesto de fórmula (I) de conformidad con la Reivindicación **1**, dicho método comprende:

Reacción de un compuesto que tiene formula II:



II

con un compuesto de fórmula (IV): $A^1-S(O)_2-Z$ en condiciones suficientes para producir un compuesto que tiene formula (VI):



(VI)

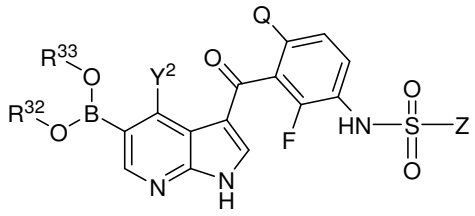
Reacción de un compuesto de fórmula (VI) con un compuesto de la fórmula: Y^1–E^2 y un compuesto de la formula: $(OR^{31})_2B$–$B(OR^{31})_2$ en presencia de un complejo de paladio en condiciones suficientes para producir el compuesto de fórmula (I), donde R^{31} es –OH, alquilo o dos sustituyentes $-OR^{31}$ junto con el átomo de boro al cual están unidos para producir un anillo de 5 o 6 miembros; y donde

E^1 y E^2 son cada uno por separado halógeno, tosilato o mesilato;

A^1 es un grupo saliente; y

P^1 es H o un grupo protector amino.

50. Un compuesto que tiene formula (VIII):



VIII

donde R^{32} y R^{33} son cada uno por separado H, alquilo sustituido opcionalmente, sustituido opcionalmente ariloalquilo o arilo sustituido opcionalmente;

Y^2, Q y Z se definen como cualquiera de las reivindicaciones **1**–**45**.

51. Un método para tratar a un sujeto que padece de una enfermedad o estado mediado por proteína quinasas o presenta un riesgo de padecerlo, dicho método comprende:

Administración a dicho sujeto de una cantidad eficaz de un compuesto de cualquiera de las reivindicaciones **1**–**45** o una composición de cualquiera de las reivindicaciones **46** o 4**7**.

52. El método de la Reivindicación **52**, donde la proteína quinasa es B-Raf y cualquiera de las mutaciones de la misma.

53. El método de la Reivindicación **52**, donde dicha enfermedad o estado se selecciona del grupo que consiste en ataque isquémico, isquemia cerebrovascular, demencia por infarto múltiple, lesión de cabeza, lesión de la médula espina, Enfermedad de Alzheimer, Enfermedad de Parkinson, esclerosis lateral amiotrófica, demencia, corea senil, Enfermedad de Huntington, enfermedad neoplásica, complicaciones con enfermedad neoplásica, hipoxia inducida por quimioterapia, tumores estromales gastrointestinales, tumores de la próstata, tumores de mastocitos, tumores de los mastocitos en perros, leucemia mieloide aguda, leucemia linfótica aguda, leucemia mieloide crónica, leucemia linfocítica crónica, mieloma múltiple, melanoma, mastocitosis, glioma, glioblastoma, astrocitoma, neuroblastoma, sarcomas, sarcomas de origen neuroectodérmico, leiomiosarcoma, carcinoma del pulmón, carcinoma de mama, carcinoma pancreático, carcinoma de colon, carcinoma hepatocelular, carcinoma renal, carcinoma del tracto genital femenino, carcinoma de células escamosas, carcinoma in situ, linfoma, linfoma histiocítico , linfoma no Hodg-

kin, Síndromes MEN2, neurofibromatosis, Neoplasia de la célula de Schwann, síndrome mielodisplásico, leucemia, angiogenesis tumoral, cáncer de tiroides, cáncer del hígado, cáncer de los huesos, cáncer de la piel, cáncer del cerebro, cáncer del sistema nervioso central, cáncer pancreático, cáncer del pulmón, cáncer pulmonar de células pequeñas, cáncer pulmonar de células no pequeñas, cáncer de mama, cáncer de colon, cáncer de vejiga, cáncer de la próstata, cáncer del tracto gastrointestinal, cáncer del endometrio, cáncer de las trompas de Falopio, cáncer testicular, cáncer ovárico, dolor de origen neuropático, dolor de origen inflamatorio, dolor agudo, dolor crónico, migraña, enfermedad cardiovascular, insuficiencia cardiaca, hipertrofia cardiaca, trombosis , síndromes de microangiopatía trombótica, ateroesclerosis, lesión por reperfusión, isquemia, isquemia cerebrovascular, isquemia del hígado, inflamación, enfermedad renal policística, degeneración macular relacionada con la edad, artritis reumatoidea, rinitis alérgica, enfermedad inflamatoria del intestino, colitis ulcerosa, Enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren, Granulomatosis de Wegener, soriasis, escleroderma, tiroiditis crónica, Enfermedad de Grave, miastenia gravis, esclerosis múltiple, osteoartritis, endometriosis, cicatrización dérmica, cicatrización de tejidos, restenosis vascular, trastornos fibróticos, hipereosinofilia, Inflamación de CNS, pancreatitis, nefritis, dermatitis atópica,

hepatitis, enfermedades provocadas por inmunodeficiencia, inmunodeficiencia combinada grave, rechazo a transplante de órganos, enfermedad de injerto contra huésped, enfermedad renal, enfermedad prostática, nefropatía diabética, nefrosclerosis, glomerulonefritis, nefritis intersticial, Nefritis lúpica, hiperplasia prostática, deficiencia renal crónica, necrosis tubular, complicación renal vinculada a diabetes, hipertrofia renal vinculada, diabetes tipo I, diabetes tipo 2, síndrome metabólico, obesidad, esteatosis hepática, resistencia a la insulina, hiperglicemia, lipolisis obesidad, infección, *Helicobacter pylori* infección, *Influenza virus* infección, fiebre, septicemia, enfermedades pulmonares, enfermedad pulmonar obstructiva crónica, síndrome de insuficiencia respiratoria aguda, asma, alergia, bronquitis, enfisema, fibrosis pulmonar, enfermedades de desarrollo genético, Síndrome de Noonan, Síndrome de Crouzon, acrocefalosindactilia tipo I, Síndrome de Pfeiffer, Síndrome de Jackson-Weiss, Síndrome de Costello, síndrome de faciocutaneoesqueletal, síndrome de Leopard, síndrome cardio-faciocutáneo, anomalías provocadas por el síndrome de crestas neurales causando enfermedades cardiovasculares, esqueletales, intestinales, de la piel, del cabello o endocrinas, trastornos de la estructura ósea o mineralización, osteoporosis, riesgo aumentado de fracturas, hipercalcemia, metástasis ósea, Enfermedad de Grave, Enfermedad de Hirschsprung, linfoedema, defecto selectivo en las células T, agamma-

globulinemia congénita, retinopatía diabética, alopecia, disfunción eréctil y esclerosis tuberosa.

54. El método de la Reivindicación **54**, donde dicha enfermedad o trastorno es seleccionado de melanoma, cáncer de tiroides o de colon.

RECEIVED
JUN 04 2012
I.P. DEPT.
FOLEY & LARDNER

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: STEPHEN REITER
FOLEY & LARDNER LLP
3579 VALLEY CENTRE DRIVE, SUITE 300
SAN DIEGO, CA 92130

PCT

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

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 31 MAY 2012
Applicant's or agent's file reference 039363-7211	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2012/023543	International filing date *(day/month/year)* 01 February 2012
Applicant PLEXXIKON INC.	

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

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
   1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

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

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

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

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

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

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

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

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

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 039363-7211	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2012/023543	International filing date *(day/month/year)* 01 February 2012	(Earliest) Priority Date *(day/month/year)* 07 February 2011
Applicant PLEXXIKON, INC.		

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

This international search report consists of a total of 3 sheets.

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

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ 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, 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. 1

   ☒ 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/US2012/023543

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.: 26, 27, 31, 33-43, 46-48, 51-55
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:

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 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/US2012/023543

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/407 (2012.01)
USPC - 514/300
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) -A61K 31/407; C07D 209/00, 221/00 (2012.01)
USPC - 514/255.05, 300; 546/113

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 practicable, search terms used)
PatBase, Orbit, SureChemOpen, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0249118 A1 (IBRAHIM et al) 30 September 2010 (30.09.2010) entire document	1-5, 7-9, 11, 12, 19, 20 24, 25, 28, 44, 45
X	US 2010/0286178 A1 (IBRAHIM et al) 11 November 2010 (11.11.2010) entire document	1, 6
X ----- Y	WO 2010/129570 A1 (VISOR et al) 11 November 2010 (11.11.2010) entire document This document can be viewed by entering the doc number at the following url: http://worldwide.espacenet.com/numberSearch?locale=en_EP	1, 8, 10, 13-18, 21-23, 29, 30, 32, 49 ---------- 50
Y	WO 2010/059658 A1 (AXTEN et al) 27 May 2010 (27.05.2010) entire document This document can be viewed by entering the doc number at the following url: http://worldwide.espacenet.com/numberSearch?locale=en_EP	50

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

* 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 application or patent 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	Date of mailing of the international search report
30 April 2012	31 MAY 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: STEPHEN REITER
FOLEY & LARDNER LLP
3579 VALLEY CENTRE DRIVE, SUITE 300
SAN DIEGO, CA 92130

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	31 MAY 2012
Applicant's or agent's file reference 039363-7211	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2012/023543	01 February 2012	07 February 2011

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/407 (2012.01)
USPC - 514/300

Applicant PLEXXIKON INC.

1. This opinion contains indications relating to the following items:

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

2. **FURTHER ACTION**

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

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	30 April 2012	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2012/023543

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ 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)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☐ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2012/023543

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 26, 27, 31, 33-43, 46-48, 51-55

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 26, 27, 31, 33-43, 46-48, 51-55 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 26, 27, 31, 33-43, 46-48, and 51-55 are multiple dependent claims not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 26, 27, 31, 33-43, 46-48, 51-55

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2012/023543

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	50	YES
	Claims	1-25, 28-30, 32, 44, 45, 49	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-25, 28-30, 32, 44, 45, 49, 50	NO
Industrial applicability (IA)	Claims	1-25, 28-30, 32, 44, 45, 49, 50	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-5, 7-9, 11, 12, 19, 20, 24, 25, 28, 44, 45 lack novelty under PCT Article 33(2) as being anticipated by Ibrahim et al. (hereafter Ibrahim; US20100249118).

Regarding claims 1-3, 12, 25 Ibrahim discloses a compound of formula I, or [Cl. 12] formula (Ie): or pharmaceutically acceptable salts, hydrates, solvates, tautomers and isomers, thereof; wherein: Y1 is an optionally substituted heteroaryl, [Cl. 3] wherein the heteroaryl group has 1 heteroatom as ring member which is N, and [Cl. 25] wherein it is a 6-member heteroaryl; Y2 is H; Q is F; Z is –C(R6)(R7)(R8), wherein R6, R7, and R8 are each independently H (compound P-1605, Pg. 206).

Regarding claim 4, 28 Ibrahim discloses the compound of claim 1, wherein Y1 is halogen; Y2 is H; Q is F; Z is –C(R6)(R7)(R8), wherein one of R6, R7, and R8 is a C2alkyl and the others are H (compound P-0919, Para. [1830]).

Regarding claims 5, 8, 9, and 24 Ibrahim discloses the compound of claim 1, having the formula (Ia), [Cl. 8] formula (Id), or [Cl. 9] formula (Id-1): wherein Y1 is an optionally substituted phenyl; Y2 is H; Q is F; Z is N(R4)(R5), wherein R4 and R5 are C1alkyls (compound P-0857, Pg. 455, Table 1).

Regarding claim 7, Ibrahim discloses the compound of claim 1, having the formula Ic: wherein Y1 is an optionally substituted heteroaryl; Y2 is H; Q is F; Z is –C(R6)(R7)(R8), wherein R6 is H, and R7 and R8 are C1alkyls (compound P-0850, Pg. 145).

Regarding claim 11, Ibrahim discloses the compound of claim 8, or isomers thereof, having formula (Id-3): wherein R12 is R1, and p=1, when R1 is Ra, which is halogen; R7 and R8 are C1alkyls (isomer compound P-1259, Pg. 121).

Regarding claim 19, Ibrahim discloses the compound of claim 1, having the formula (Ih): wherein Z1 is S; R16 is H; Y2 is H; Q is H; Z is –C(R6)(R7)(R8), wherein two of R6, R7, and R8 is a C2alkyl and the other is H (formula II, Para. [0119], wherein R4, R6, R14, R15 and R16 are hydrogen and A is -C(O)-, R12 is -F, R5 is thiophen-2-yl, R13 is -LR24, when L is –(alk)a-NR25S(O)2-(alk)b- Para. [0197]; a and b are independently 0 or 1, Para. [0017], R24 is C2alkyl, Para [0030], alk is C2 alkylene, Para. [0018], and R25 is hydrogen, Para. [0023]).

Regarding claim 20, Ibrahim discloses the compound of claim 1, having the formula (Ii): wherein R17 is H; R18 is H; R16 is H; Y2 is H; Q is H; Z is –C(R6)(R7)(R8), wherein one of R6, R7, and R8 is a C2alkyl and the others are H (formula IIf, Pg. 30, when A is -C(O)-, R14, R15 andR16 are hydrogen and R12 is halogen, Para. [0233]; R5 is other than hydrogen and R4 and R6 are hydrogen, Para. [0210], when R5 is an optionally substituted heteroaryl, Para. [0010]; wherein heteroaryl is defined as pyrrolyl, Para. [0670]; wherein R24 is as defined for formula I, Para [0122], when R24 is C2alkyl, Para [0030]).

Regarding claim 44, Ibrahim discloses compound P-0117 as set forth in Table 2 or pharmaceutically acceptable salts, hydrates, solvates, tautomers and isomers thereof (formula IIg, Pg. 30, when A is -C(O)-, R14, R15 andR16 are hydrogen and R12 is halogen, Para. [0233]; R5 is other than hydrogen and R4 and R6 are hydrogen, Para. [0210], when R5 is halogen, Para [0010]; wherein R24 is as defined for formula I, Para [0122], when R24 is C3alkyl, Para [0030]).

Regarding claim 45, Ibrahim discloses compound P-0118 as set forth in table 3 or pharmaceutically acceptable salts, hydrates, solvates, solvates, tautomers and isomers thereof (formula IIg, Pg. 30, when A is -C(O)-, R14, R15 andR16 are hydrogen and R12 is halogen, Para. [0233]; R5 is other than hydrogen and R4 and R6 are hydrogen, Para. [0210], when R5 is an optionally substituted heteroaryl, Para. [0010]; wherein heteroaryl is defined as pyrimidinyl with –ORo substituent, when Ro is alkyl, Paras. [0670]-[0671]; wherein R24 is as defined for formula I, Para [0122], when R24 is optionally substituted aryl, Para [0030], wherein aryl is defined as monocyclic aromatic hydrocarbon such as phenyl, Para. [0669]).

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US2012/023543

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of:

Claims 1, 6 lack novelty under PCT Article 33(2) as being anticipated by Ibrahim et al. (hereafter Ibrahim; US20100286178).

Regarding claim 1, Ibrahim discloses the compound of formula I: wherein: Y1 is CN; Y2 is H; Q is F; Z is –C(R6)(R7)(R8), wherein one of R6, R7, and R8 is C2alkyl and the other two are H (compound P-0002, Pg. 16).

Regarding claim 6, Ibrahim discloses the compound of claim 1, having the formula Ib: wherein Y1 is CN; Y2 is H; Q is F; Z is N(R4)(R5), wherein R4 and R5 taken together with the nitrogen atom to which they are attached to form a 5 member ring, when n=2 and m=0 (compound P-0006, Pg. 21).

Claims 1, 8, 10, 13-18, 21-23, 29, 30, 32, 49 lack novelty under PCT Article 33(2) as being anticipated by Visor et al. (hereafter Visor).

Regarding claims 1, Visor discloses the compound of formula I, wherein Y1 is an optionally substituted aryl, when R12 is R1 and p=2, when R1 is independently selected from C1haloalkyl and -Ra, wherein Ra is halogen; Y2 is H; Q is F; Z is –C(R6)(R7)(R8), wherein one of R6, R7, and R8 is C2alkyl and the other two are H (compound P-2160, Pg. 224).

Regarding claim 8, Visor discloses the compound of claim 1, having formula (id): wherein R12 is R1 and p=2, when R1 is independently selected from C1alkoxy and -Ra, wherein Ra is halogen (compound P-2159, Pg. 224).

Regarding claim 10, Visor discloses the compound of claim 8, having formula (Id-2): wherein R12 is R1, and p=1, when R1 is Ra, and Ra is halogen (pyrrolidine-1-sulfonic acid [3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluorophenyl]-amide (P-2425), Pg. 63).

Regarding claim 13, Visor discloses the compound of claim 1 or isomers thereof, having the formula (If): wherein R14 is R1, and r=1, when R1 is C1alkoxy; Y2 is H; Q is F; Z is –C(R6)(R7)(R8), wherein one of R6, R7, and R8 is C2alkyl and the other two are H (compound P-1496 corresponds to an isomer of formula If, because the pyrimidine ring is an isomer of the claimed pyrazine ring group, Pg. 232)

Regarding claims 14, 15, and 18, Visor discloses the compound of claim 1, having formula (Ig): wherein R15 is R1, and s=1, when R1 is C1alkoxy; Y2 is H; Q is H; Z is –C(R6)(R7)(R8), wherein one of R6, R7, and R8 is C2alkyl and the other two are H (compound P-2407, Pg. 231).

Regarding claims 16 and 17, Visor discloses the compound of claims 14 or 15, wherein Z is N(R4)(R5), wherein R4 and R5 taken together with the nitrogen atom to which they are attached to form a 5 member ring, when n=2 and m=0 (compound P-2422, Pg. 231).

Regarding claim 21, Visor discloses the compound of claim 1 or isomer thereof, having formula (Ij): wherein R19 is C1alkyl; R20 is R1, and v=1, when R1 is C1alkyl; Y2 is H; Q is F; Z is –C(R6)(R7)(R8), wherein one of R6, R7, and R8 is C2alkyl and the other two are H (compound 2152, Pg. 237).

Regarding claims 22 and 23, Visor discloses the compound of claim 1, having formula (Ik) or (Il): wherein R22 is R1, and x=2, when R1 is C1alkyl;[Cl. 22] Z2 is O; [Cl. 23] Z3 is O; Y2 is H; Q is F; Z is –C(R6)(R7)(R8), wherein one of R6, R7, and R8 is C2alkyl and the other two are H (compound P-2156 corresponding to formula (Il) or isomer thereof, where the isoxazole ring is an isomer of the oxazole ring in formula (Ik), Pg. 223).

Regarding claim 29, Visor discloses the compound of claim 1, wherein Y1 is 2-methoxy-pyrimidin-5-yl (propane-1-sulfonic acid {2-fluoro-3-[5-(2-methoxy-pyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (P-2407), Pg. 54).

Regarding claim 30, 32 Visor discloses the compound of claim 1, wherein Y1 is 4-halophenyl; and [Cl. 32] wherein Y2 is H (pyrrolidine-1-sulfonic acid [3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluorophenyl]-amide (P-2425), Pg. 63).

Regarding claim 49, Visor discloses a method of preparing a compound of formula (I) according to claim 1, said method comprising: contacting a compound having formula II with an agent of formula (III): Y1-G1 under condition sufficient to form a compound of formula (V), wherein E1 is halogen, P1 is H, and G1 is –B(OR25)2, wherein R25 is –OH, wherein said contacting or reacting with the agent of formula (III) is in the presence of a palladium complex (reaction of compound 19 and compound 20 to produce compound 21, Para. [0222]), in a vial containing [1,1'-bis(diphenylphosphino)ferrocene]dichloro palladium (II), Para. [0223]; and reacting a compound of formula (V) with a compound formula (IV) A1-S(O)2-Z, wherein A1 is a leaving group (compound equivalent to compound 21 reacted with an appropriate sulfonyl chloride forming compound P-2295, Pg. 203).

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2012/023543

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Claim 50 lacks an inventive step under PCT Article 33(3) as being obvious over Visor in view of Axten et al. (hereafter Axten).

Regarding claim 50, Visor discloses a method of preparing a compound of formula (I) according to claim 1, said method comprising: reacting a compound of formula (II) with a compound formula (IV) A1-S(O)2-Z, wherein wherein E1 is halogen, P1 is H, and A1 is a leaving group, under conditions sufficient to form a compound having formula (VI) (scheme 4, reacting compound 8 with sulfonyl chloride 46, Para. [0234]; additional compounds were prepared similarly by optionally replacing 46 with an appropriate sulfonyl chloride, Para. [0237]). However, Visor lacks the teaching of reacting a compound of formula (VI) with a compound of formula Y1-E2, wherein Y1 is an optionally substituted heteroaryl and E2 is halogen, and a compound of formula (OR31)2B-B(OR31)2 in the presence of a palladium catalyst, wherein two –OR31 substiuents together with the boron atom to which they are attached to form a 5-membered ring. Axten is in the field 6-(4-pyrinidinyl)-1H-indazole derivatives used as kinase inhibitors (Pg. 1 lines 4-7). Axten teaches a substitution reaction on a halogenated aromatic ring system using a compound of formula Y1-E2, wherein Y1-E2, wherein Y1 is an optionally substituted heteroaryl and E2 is halogen, and a compound of formula (OR31)2B-B(OR31)2 in the presence of a palladium catalyst, wherein two –OR31 substiuents together with the boron atom to which they are attached to form a 5-membered ring (scheme 3 reaction compound 13 with bispinacolatodiboron and compound 3 to produce compound 10, Pg. 52; wherein the bispinacolatodiboron coupling can be carried out using a palladium catalyst, Pg. 52 lines 18-22). It would have been obvious to one of ordinary skill in the art at the time of the invention to utilize a substitution reaction of Axten in the process of Visor. The motivation would have been to substitute the halogen on the pyridine ring with an appropriate desired group in a one step in situ coupling reaction (Pg. 52 lines 14-22, Axten).

Claims 1-25, 28-30, 32, 44, 45, 49, 50 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.