SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-081901- -00000-0000

Fecha. 2012-05-17 16:43:40 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 271

Act. 411 PRESENTACION Folios: 270

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 CINASAS, E INDICACIONES PARA ELLO

SOLICITANTE: PLEXXIKON, INC.

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

APODERADO: CARLOS R. OLARTE

BOGOTÁ 17 de Mayo de 2012

P2012/000063

OLARTE

OLARTE MOURE & AS

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-081901- -00000-0000

Fecha: 2012-05-17 16:43:40 Dep. 2020 DIR.NUEVASCR
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Act. 411 PRESENTACION Folios: 270

Industria y Comercio
SUPERINTENDENCIA

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2012/000063**

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 Bolivar 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/US2010/057293 Fecha Noviembre 18, 2010

Publicación Internacional No. WO 2011/063159 Fecha Mayo 26, 2011

(6) **Título (54)** **COMPUESTOS Y MÉTODOS PARA LA MODULACIÓN DE CINASAS, E INDICACIONES PARA ELLO**

Clasificación Internacional (51) A01N 43/90; A61K 31/519.

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Noviembre 18, 2009	61/262.510
US	Septiembre 15, 2010	61/383, 310

(9) **Comprobante de pago No.** 12-0048270 **Fecha** Mayo 16 de 2012

LISTA DE INVENTORES

PCT/US2010/057293

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

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

Hanna CHO
425 Orange Street, # 314
Oakland, CA 94610
Estados Unidos de América
Nacionalidad: Estadounidense

Songyuan SHI
4347 Othello Drive
Fremont, CA 94555
Estados Unidos de América
Nacionalidad: Estadounidense

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

Ying ZHANG
39201 Red Hawk Terrace, # a204
Fremont, CA 94538
Nacionalidad: República Popular de China

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0048270

Bogotá D.C., Mayo 16 de 2012 - 10:13:13

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	455546254	15/05/2012	2.960.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	590.000.00	590.000.00
				$590.000.00

SON: **QUINIENTOS NOVENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-*-
Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-081901- -00000-0000

Fecha: 2012-05-17 16:43:40 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 271

Act. 411 PRESENTACION Folios: 270

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

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

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 Ministerio

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

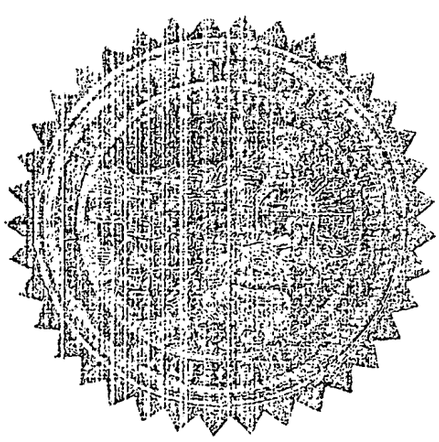
(Convention de La Haye du 5 octobre 1961)

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





Secretary of State

BY

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

Branch Offices Available To Serve You

CHULA VISTA
...00 Third Avenue
...la 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

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

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

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

Of Counsel
Guillermo Chahin
Graciela Melo

Power of Attorney

Poder

The undersigned,

El suscrito,

PLEXXIKON, INC.

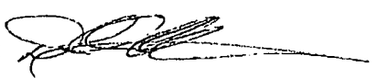
domiciled in

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

OLARTE RAISBECK
OLARTE RAISBECK & FRIERI LTDA.

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

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

1. That

of legal age and domiciled in
Dean R. Artis
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 leyès 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 - 1003

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*

Secretary of State

BY

HI-24 A (REV 4-05)

OSP 05 90772

10

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

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CERTIFICATE OF THE PRESIDENT AND SECRETARY

OF

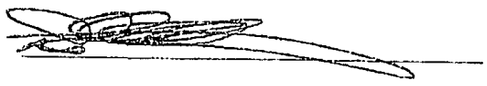
PLEXXIKON INC.
91 Bolivar Drive
Berkeley, CA 94710

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

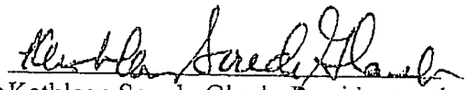
1. She is the duly elected, qualified and acting President and Secretary of Plexxikon Inc. a California corporation (the "***Company***"), and is familiar with the facts herein certified and is duly authorized to certify the same, and to make the statements as certified by her herein.

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 SEREDA GLASS (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.

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

Signature of Notary Public

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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 ver expediente No. 08-033466.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [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.
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- [ ] 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.
- [x] 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:

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(74) Agent: **REITER, Stephen, E.**; Foley & Lardner LLP, 3579 Valley Centre Drive, Suite 300, San Diego, California 92130 (US).

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

(57) Abstract: Compounds and salts thereof, formulations thereof, conjugates thereof, derivatives thereof, forms thereof and uses thereof are described. In certain aspects and embodiments, the described compounds or salts thereof, formulations thereof, conjugates thereof, derivatives thereof, forms thereof are active on at least one Raf protein kinase. In certain aspects and embodiments, the described compounds are active in inhibiting proliferation of a Ras mutant cell line. Also described are methods of use thereof to treat diseases and conditions, including diseases and conditions associated with activity of B-Raf V600E mutant protein kinase, including 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. Also described are methods of use thereof to treat diseases and conditions, including diseases and conditions associated with activity of c-Raf-1 protein kinase, including acute pain, chronic pain or polycystic kidney disease.

COMPOUNDS AND METHODS FOR KINASE MODULATION, AND INDICATIONS THEREFOR

FIELD OF THE INVENTION

[0001] Disclosed are novel compounds and uses thereof. In certain embodiments disclosed compounds are kinase inhibitors.

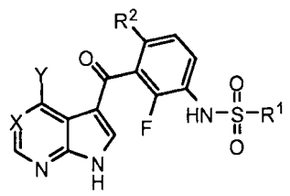
SUMMARY OF THE INVENTION

[0002] In certain aspects and embodiments disclosed herein, compounds are provided, as well as various salts thereof, formulations thereof, conjugates thereof, derivatives thereof, forms thereof and uses thereof. In some embodiments, compounds are of Formula I, Formula II, Formula III and Formula IIIa as described below. In certain embodiments, the compounds inhibit one or more Raf protein kinases, including one or more of A-Raf, B-Raf, and c-Raf-1, and any mutations thereof. In certain embodiments, the compounds inhibit c-Raf-1 protein kinase. In certain embodiments, the compounds inhibit c-Raf-1 protein kinase selectively to other Raf protein kinases. In certain embodiments, the compounds inhibit a B-Raf V600X mutant protein kinase (where X is an amino acid other than valine, e.g., alanine, arginine, aspartic acid, glycine, lysine or methionine). In certain embodiments, the compounds inhibit a B-Raf V600E mutant protein kinase. In certain embodiments, the compounds inhibit a B-Raf V600E mutant protein kinase selectively relative to other Raf protein kinases, including B-Raf protein kinase. In certain embodiments, the compounds inhibit each of c-Raf-1, B-Raf, B-Raf V600X, and B-Raf V600E protein kinase.

[0003] Also contemplated in accordance with the present invention are methods for the use of the compounds in treating diseases and conditions associated with regulation of the activity of one or more Raf protein kinases, including one or more of A-Raf, B-Raf, and c-Raf-1, and any mutations thereof. Thus, the use of compounds for therapeutic methods involving modulation of protein kinases are provided. In certain embodiments, the compounds inhibit the activity on one or more Raf kinases, including A-Raf, B-Raf and/or c-Raf-1, including any mutations thereof. In certain embodiments, the compounds are used for therapeutic methods involving modulation of one or more Raf protein kinases, including treatment of a variety of indications, including, but not limited to, 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. In certain embodiments, the compounds are used for therapeutic methods involving modulation of B-Raf V600E mutant protein kinase, including treatment of a variety of indications, including, but not limited to, 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 certain embodiments, the compounds are used for therapeutic methods involving modulation of c-Raf-1 protein kinase, including treatment of a variety of indications, including, but not limited to, acute pain, chronic pain and polycystic kidney disease.

[0004] In a first aspect, compounds having the structure according to the following Formula I are provided:



Formula I

or a pharmaceutically acceptable salt thereof,

wherein:

X is –N= or –C(R^5)=;

Y is selected from the group consisting of fluoro, chloro, bromo, iodo, lower alkyl, lower alkoxy, haloalkyl, CN, -OH, fluoro substituted alkyl, cycloalkyl, -OR^8, and –N(R^3)-R^4;

R^1 is selected from the group consisting of lower alkyl, haloalkyl, haloalkoxy, fluoro substituted lower alkyl, cycloalkyl optionally substituted with one or more R^7, heterocycloalkyl, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, aryl optionally substituted with one or more R^6 (e.g., R^1 is 2-fluoro-substituted phenyl, 3-fluoro-substituted phenyl, 2,5-difluoro-substituted phenyl or 4-lower alkyl-substituted phenyl, wherein lower alkyl is optionally substituted with one or more fluorine), and heteroaryl optionally substituted with one or more R^7;

R^2 is hydrogen, fluoro, chloro or lower alkyl optionally substituted with one or more fluorine;

R^3 is hydrogen and R^4 is selected from the group consisting of hydrogen, -OR^8, lower alkyl optionally substituted with one or more R^{11}, cycloalkyl optionally substituted with one or more R^{12},

cycloalkylalkyl optionally substituted with one or more R^{12}, heterocycloalkyl optionally substituted with one or more R^{13}, heterocycloalkylalkyl optionally substituted with one or more R^{13}, aryl optionally substituted with one or more R^{14}, arylalkyl optionally substituted with one or more R^{14}, and heteroaryl optionally substituted with one or more R^{15};

or R^3 and R^4 are both lower alkyl;

or R^3 and R^4 combine with the nitrogen to which they are attached to form cycloalkylamino or R^3 and R^4 combine with the nitrogen atom to which they are attached to form a 3-7 membered ring having 0-1 additional heteroatom selected from O or N;

R^5 is selected from the group consisting of hydrogen, fluoro, chloro, -CN, lower alkyl optionally substituted with one or more R^{16}, and lower alkoxy optionally substituted with one or more R^{17};

each R^6, when present, is independently selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, $-C(O)-O-R^{18}$, $-N(H)-C(O)-R^{19}$, and heteroaryl optionally substituted with one or more lower alkyl; or two R^6 on adjacent carbons combine to form a fused heterocycloalkyl optionally substituted with one or more lower alkyl;

each R^7, when present, is independently selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, lower alkoxy, $-C(O)-O-R^{20}$, and heteroaryl optionally substituted with one or more lower alkyl;

R^8 is hydrogen, lower alkyl optionally substituted with one or more fluorine, or, when R^8 is a C_{2-6} alkyl, said alkyl may optionally be substituted with one or more R^{21}; cycloalkyl optionally substituted with one or more R^{21}, or heterocycloalkyl optionally substituted with one or more R^{21};

each R^{11}, when present, is independently selected from the group consisting of fluoro, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, cycloalkyl optionally substituted with one or more R^{12}, heterocycloalkyl optionally substituted with one or more R^{13}, aryl optionally substituted with one or more R^{14}, and heteroaryl optionally substituted with one or more R^{15};

each R^{12}, when present, is independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, $-N(H)-C(O)-R^{22}$, $-N(H)-S(O)_2-R^{23}$, $C(O)-R^{24}$, and $S(O)_2-R^{25}$;

each R^{13}, when present, is independently selected from the group consisting of fluoro, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino,

cycloalkylamino, heterocycloalkylamino, -N(H)-C(O)-R^{26}, -N(H)-$S(O)_2$-R^{27}, C(O)-R^{28}, $S(O)_2$-R^{29}, and lower alkyl optionally substituted with one or more R^{30};

each R^{14} and R^{15}, when present, are independently selected from the group consisting of fluoro, chloro, -OH, $-NH_2$, -CN, $-NO_2$, -N(H)-C(O)-R^{31}, -N(H)-$S(O)_2$-R^{32}, C(O)-R^{33}, $S(O)_2$-R^{34}, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, aryl optionally substituted with one or more R^{35}, and heteroaryl optionally substituted with one or more R^{36};

each R^{16}, when present, is independently fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{17}, when present, is independently fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{18} and R^{20}, when present, are independently hydrogen, lower alkyl or fluoro substituted lower alkyl;

each R^{19}, R^{22}, R^{23}, R^{26}, R^{27}, R^{31} and R^{32}, when present, are independently lower alkyl or fluoro substituted lower alkyl;

each R^{21}, when present, is fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{24}, R^{25}, R^{28}, R^{29}, R^{33}, and R^{34}, when present, are independently lower alkyl, fluoro substuted lower alkyl, -OH, lower alkoxy, fluor substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{30}, when present, is independently fluoro, aryl optionally substituted with one or more R^{35} or heteroaryl optionally substituted with one or more R^{36}; and

each R^{35} and R^{36}, when present, are independently selected from the group consisting of fluoro, chloro, -OH, $-NH_2$, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino.

[0005] In some embodiments of compounds of Formula I:

X is -N= or –C(R^5)=; wherein R^5 is selected from the group consisting of hydrogen, fluoro, chloro, -CN, lower alkyl and lower alkoxy, wherein the lower alkyl or lower alkoxy is optionally substituted with from one to three groups selected from fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino.

Y is selected from the group consisting of fluoro, chloro, bromo, iodo, lower alkyl, lower alkoxy, haloalkyl (e.g., fluoro substituted alkyl), CN, -OH, cycloalkyl, $-OR^8$, and $-N(R^3)-R^4$;

R^1 is selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, cycloalkyl, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, phenyl optionally substituted with from one to three R^6 (e.g., R^1 is 2-fluoro-substituted phenyl, 3-fluoro-substituted phenyl, 2,5-difluoro-substituted phenyl or 4-lower alkyl-substituted phenyl, wherein lower alkyl is optionally substituted with from one to three fluorine atoms), and heteroaryl optionally substituted with one to three R^7;

R^2 is hydrogen, fluoro, chloro, or lower alkyl optionally substituted with one or more fluorine;

R^3 is hydrogen and R^4 is selected from the group consisting of (i) hydrogen, $-OR^8$ and lower alkyl optionally substituted with from one to three R^{11}; (ii) cycloalkyl or cycloalkylalkyl, each of which is optionally substituted with from one to three R^{12}; (iii) heterocycloalkyl or heterocycloalkylalkyl, each of which is optionally substituted with from one to three R^{13}; (iv) aryl or arylalkyl, each of which is optionally substituted with from one to three R^{14} optionally, wherein the two adjacent R^{14} groups on the aryl ring are taken together to form a 5 or 6-membered hetero aromatic ring having from 1-4 heteroatoms selected from O or N; and (v) heteroaryl or heteroarylalkyl, each of which is optionally substituted with from one to three R^{15};

or R^3 and R^4 are both lower alkyl;

or R^3 and R^4 combine with the nitrogen atom to which they are attached to form a three to seven membered ring having 0-1 additional heteroatom selected from O, N or S, wherein the nitrogen and sulfur atoms are optionally oxidized;

each R^6, when present, is independently selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, $-C(O)-O-R^{18}$, $-N(H)-C(O)-R^{19}$, and heteroaryl optionally substituted with one or more lower alkyl; or two R^6 on adjacent carbons combine to form a fused heterocycloalkyl optionally substituted with one or more lower alkyl;

each R^7, when present, is independently selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, lower alkoxy, $-C(O)-O-R^{20}$, and heteroaryl optionally substituted with one or more lower alkyl;

R^{11}, when present, is selected from the group consisting of cycloalkyl, -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino;

each R^{14} and R^{15}, when present, are independently selected from the group consisting of fluoro, chloro, -CN, -NO_2, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy;

each R^{18}, when present, is independently hydrogen or lower alkyl;

each R^{19}, when present, is independently lower alkyl; and

each R^{20}, when present, is independently hydrogen or lower alkyl.

[0006] In some embodiments of compounds of Formula I, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like. In some embodiments, R^1 is lower alkyl or cycloalkyl (e.g., cyclopropyl), preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like. In some embodiments of compounds of Formula I, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like; and R^2 is hydrogen. In some embodiments of compounds of Formula I, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like; and R^2 is fluoro. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0007] In some embodiments, X is selected from the group consisting of –N=, –CH=, -C(CH_3)=, -C(OCH_3)=, -C(F)=, -C(CN)=, -C(CH_2OH)= and –C(Cl)=. In certain instances, X is –N=, –CH=, -C(CH_3)=, -C(F)= or -C(CN)=. In a preferred embodiment, X is –N=. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0008] In some embodiments of compounds of Formula I, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like. In some embodiments, R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like; and R^2 is hydrogen. In some embodiments of compounds of Formula I, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like; and R^2 is fluoro. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0009] In some embodiments of compounds of Formula I, Y is -OR^8; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like. In some embodiments, R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like, and R^8 is hydrogen, lower alkyl optionally substituted with one or more

fluorine, or cycloalkyl optionally substituted with one or more fluorine. In some embodiments, R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like, and R^8 is hydrogen, lower alkyl optionally substituted with one or more fluorine, or cycloalkyl optionally substituted with one or more fluorine; and R^2 is hydrogen. In some embodiments, R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like, and R^8 is hydrogen or lower alkyl ; and R^2 is fluoro. All the other variables are as defined in any of the above embodiments, or as described hereinafter.

[0010] In some embodiments of compounds of Formula I, Y is $-N(R^3)-R^4$; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like. In some embodiments of compounds of Formula I, $Y-N(R^3)-R^4$; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like; and R^2 is hydrogen. In some embodiments of compounds of Formula I, $Y-N(R^3)-R^4$; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like; and R^2 is fluoro. In some embodiments, R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like, R^3 is hydrogen and R^4 is selected from the group consisting of hydrogen, -OH, lower alkyl optionally substituted with R^{11}, cycloalkyl, heterocycloalkyl optionally substituted with lower alkyl, phenyl optionally substituted with one or more R^{14}, and 5-6 membered heteroaryl optionally substituted with one or more lower alkyl, or R^3 and R^4 are both lower alkyl, or R^3 and R^4 combine with the nitrogen to which they are attached to form a three to seven membered ring having 0-1 additional heteroatom selected from O, N or S, wherein the nitrogen and sulfur atoms are optionally oxidized, wherein R^{11} and R^{14} are as defined for Formula I, preferably wherein R^{11} is selected from the group consisting of cycloalkyl, -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino and R^{14} is selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0011] In some embodiments of compounds of Formula I, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino. In some embodiments of compounds of Formula I, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino; and R^2 is hydrogen. In some embodiments of compounds of Formula I, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino,

preferably di-alkylamino or cycloalkylamino; and R^2 is fluoro. In some embodiments, R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0012] In some embodiments of compounds of Formula I, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino. In some embodiments of compounds of Formula I, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino ; and R^2 is hydrogen. In some embodiments, R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino ; and R^2 is fluoro. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0013] In some embodiments of compounds of Formula I, Y is $-OR^8$; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino. In some embodiments of compounds of Formula I, Y is $-OR^8$; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino; and R^2 is hydrogen. In some embodiments of compounds of Formula I, Y is $-OR^8$; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino; and R^2 is fluoro. In some embodiments, R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino, and R^8 is hydrogen or lower alkyl. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0014] In some embodiments of compounds of Formula I, Y is $-N(R^3)-R^4$; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino. In some embodiments of compounds of Formula I, Y is $-N(R^3)-R^4$; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino ; and R^2 is hydrogen. In some embodiments of compounds of Formula I, Y is $-N(R^3)-R^4$; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino ; and R^2 is fluoro. In some embodiments, R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino, R^3 is hydrogen and R^4 is selected from the group consisting of hydrogen, -OH, lower alkyl optionally substituted with R^{11}, cycloalkyl, heterocycloalkyl optionally substituted with lower alkyl, phenyl optionally substituted

with one or more R^{14}, and 5-6 membered heteroaryl optionally substituted with one or more lower alkyl, or R^3 and R^4 are both lower alkyl, or R^3 and R^4 combine with the nitrogen to which they are attached to form cycloalkylamino, wherein R^{11} and R^{14} are as defined for Formula I, preferably wherein R^{11} is selected from the group consisting of cycloalkyl, -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino, and R^{14} is selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0015] In some embodiments of compounds of Formula I, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. In some embodiments of compounds of Formula I, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and R^2 is hydrogen. In some embodiments of compounds of Formula I, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and R^2 is fluoro. In some embodiments, R^1 is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy. In some embodiments, R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0016] In some embodiments of compounds of Formula I, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. In some embodiments of compounds of Formula I, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and R^2 is hydrogen. In some embodiments of compounds of Formula I, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro

substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and R^2 is fluoro. In some embodiments, R^1 is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy. In some embodiments, R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0017] In some embodiments of compounds of Formula I, Y is $-OR^8$; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. In some embodiments of compounds of Formula I, Y is $-OR^8$; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and R^2 is hydrogen. In some embodiments of compounds of Formula I, Y is $-OR^8$; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and R^2 is fluoro. In some embodiments, R^1 is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy. In some embodiments, R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy, and R^8 is hydrogen or lower alkyl. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0018] In some embodiments of compounds of Formula I, Y is $-N(R^3)-R^4$; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. In some embodiments, R^1 is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy. In some embodiments of compounds of Formula I, Y is $-N(R^3)-R^4$; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and R^2 is hydrogen. In some embodiments, R^1 is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy; and R^2 is fluoro. In some embodiments, R^1 is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy. In some embodiments, R^1 is phenyl optionally substituted with 1 or 2 substituents

independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy, R^3 is hydrogen and R^4 is selected from the group consisting of hydrogen, -OH, lower alkyl optionally substituted with R^{11}, cycloalkyl, heterocycloalkyl optionally substituted with lower alkyl, phenyl optionally substituted with one or more R^{14}, and 5-6 membered heteroaryl optionally substituted with one or more lower alkyl, or R^3 and R^4 are both lower alkyl, or R^3 and R^4 combine with the nitrogen to which they are attached to form cycloalkylamino wherein R^{11} and R^{14} are as defined for Formula I, preferably wherein R^{11} is selected from the group consisting of cycloalkyl, -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino, and R^{13} is selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. In some embodiments, R^1 is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy, R^3 is hydrogen and R^4 is selected from the group consisting of hydrogen, -OH, lower alkyl optionally substituted with R^{11}, cycloalkyl, heterocycloalkyl optionally substituted with lower alkyl, phenyl optionally substituted with one or more R^{14}, and 5-6 membered heteroaryl optionally substituted with one or more lower alkyl, or R^3 and R^4 are both lower alkyl, or R^3 and R^4 combine with the nitrogen to which they are attached to form cycloalkylamino, wherein R^{11} and R^{14} are as defined for Formula I, preferably wherein R^{11} is selected from the group consisting of cycloalkyl, -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino, and R^{14} is selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0019] In some embodiments of compounds of Formula I, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy. In some embodiments of compounds of Formula I, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is hydrogen. In some embodiments of compounds of Formula I, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is fluoro. In some embodiments, R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2

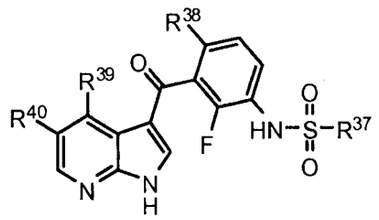
substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0020] In some embodiments of compounds of Formula I, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy. In some embodiments of compounds of Formula I, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is hydrogen. In some embodiments of compounds of Formula I, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is fluoro. In some embodiments, R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0021] In some embodiments of compounds of Formula I, Y is $-OR^8$; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy. In some embodiments of compounds of Formula I, Y is $-OR^8$; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is hydrogen. In some embodiments of compounds of Formula I, Y is $-OR^8$; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is fluoro. In some embodiments, R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy, and R^8 is hydrogen or lower alkyl. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0022] In some embodiments of compounds of Formula I, Y is $-N(R^3)-R^4$; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy. In some embodiments of compounds of Formula I, Y is $-N(R^3)-R^4$; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is hydrogen. In some embodiments of compounds of Formula I, Y is $-N(R^3)-R^4$; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is fluoro. In some embodiments, R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy, R^3 is hydrogen and R^4 is selected from the group consisting of hydrogen, -OH, lower alkyl optionally substituted with R^{11}, cycloalkyl, heterocycloalkyl optionally substituted with lower alkyl, phenyl optionally substituted with one or more R^{14}, and 5-6 membered heteroaryl optionally substituted with one or more lower alkyl, or R^3 and R^4 are both lower alkyl, or R^3 and R^4 combine with the nitrogen to which they are attached to form cycloalkylamino, wherein R^{11} and R^{14} are as defined for Formula I, preferably wherein R^{11} is selected from the group consisting of cycloalkyl, -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino, and R^{14} is selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. All the other variables are as defined in any of the above embodiments or as described hereinafter.

[0023] In a second aspect, compounds having the structure according to the following Formula II are provided:



Formula II

or a pharmaceutically acceptable salt thereof,

wherein:

R^{37} is selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, cycloalkyl, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, phenyl optionally

substituted with one or more R^{41} (e.g., R^{37} is 2-fluoro-substituted phenyl, 3-fluoro-substituted phenyl, 2,5-difluoro-substituted phenyl or 4-lower alkyl-substituted phenyl, wherein lower alkyl is optionally substituted with one or more fluorine), and heteroaryl optionally substituted with one or more R^{42};

R^{38} is hydrogen, fluoro, chloro, or lower alkyl optionally substituted with one or more fluorine;

R^{39} and R^{40} are independently selected from the group consisting of fluoro, chloro, -CN, -OH, $-NH_2$, lower alkyl optionally substituted with one or more R^{43}, lower alkenyl optionally substituted with $C(O)-O-R^{44}$, lower alkynyl optionally substituted with lower alkyl optionally substituted with one or more fluorine, or, on a non-alkynyl carbon thereof, R^{45}, lower alkoxy optionally substituted with R^{46}, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino;

each R^{41}, when present, is independently selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, $-C(O)-O-R^{47}$, $-N(H)-C(O)-R^{48}$, and heteroaryl optionally substituted with one or more lower alkyl; or two R^{41} on adjacent carbons combine to form a fused heterocycloalkyl optionally substituted with one or more lower alkyl;

each R^{42}, when present, is independently selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, $-C(O)-O-R^{49}$, and heteroaryl optionally substituted with one or more lower alkyl;

each R^{43}, when present, is independently selected from the group consisting of fluoro, -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino;

each R^{44}, when present, is independently hydrogen or lower alkyl optionally substituted with one or more fluorine;

each R^{45}, when present, is independently selected from the group consisting of -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino;

each R^{46}, when present, is independently selected from the group consisting of -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino;

each R^{47}, when present, is independently hydrogen or lower alkyl optionally substituted with one or more fluorine;

each R^{48}, when present, is independently lower alkyl optionally substituted with one or more fluorine; and

each R^{49}, when present, is independently hydrogen or lower alkyl optionally substituted with one or more fluorine.

[0024] In some embodiments of compounds of Formula II, R^{37} is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like. In some embodiments, R^{37} is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like, R^{39} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy, and R^{40} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy. In some embodiments, R^{37} is lower alkyl, fluoro substituted lower alkyl or phenyl, optionally substituted with from 1-3 R^{41} groups. In other embodiments, R^{37} is lower alkyl, fluoro substituted lower alkyl or phenyl substituted with from 1-3 groups selected from fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, $-C(O)-O-R^{47}$ or $-N(H)-C(O)-R^{48}$. In yet other embodiments, R^{37} is lower alkyl or phenyl substituted with from 1-2 groups selected from fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy or fluoro substituted lower alkoxy. In some embodiments, R^{37} is lower alkyl or phenyl optionally substituted with 1-2 members selected from CF_3 or halogen. In other embodiments, R^{37} is propyl. In yet other embodiments, R^{37} is 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl or 2,5-difluoro-substituted phenyl. All the other variables are as defined in any of the embodiments of the compounds of Formula II described herein.

[0025] In some embodiments of compounds of Formula II, R^{37} is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino. In some embodiments, R^{37} is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino, R^{39} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy, and R^{40} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy. In some embodiments, R^{37} is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino, R^{39} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy, and R^{40} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy; and R^{38} is hydrogen. In some embodiments, R^{37} is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino, R^{39} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy, and R^{40} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy; and R^{38} is fluoro. All the other variables are as defined in any of the embodiments of the compounds of Formula II described herein.

[0026] In some embodiments of compounds of Formula II, R^{37} is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. In some embodiments, R^{37} is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro,

lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy, R^{39} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy, and R^{40} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy. In some embodiments, R^{37} is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy. In some embodiments, R^{37} is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy, R^{39} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy, and R^{40} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy. In some embodiments, R^{37} is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy, R^{39} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy, and R^{40} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy; and R^{38} is hydrogen. In some embodiments, R^{37} is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy, R^{39} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy, and R^{40} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy; and R^{38} is fluoro. In some embodiments, R^{37} is 4-trifluoromethylphenyl, 2-fluorophenyl, 3-fluorophenyl or 2,5-difluoro-substituted phenyl. All the other variables are as defined in any of the embodiments of the compounds of Formula II described herein.

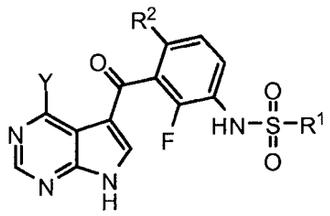
[0027] In some embodiments of compounds of Formula II, R^{37} is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy. In some embodiments, R^{37} is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy, R^{39} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy, and R^{40} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy. In some embodiments, R^{37} is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy, R^{39} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy, and R^{40} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy; and R^{38} is hydrogen. In some embodiments, R^{37} is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy, R^{39} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy, and R^{40} is fluoro, chloro, -CN, lower alkyl, or lower alkoxy; and R^{38} is fluoro.

[0028] In some embodiments of compounds of Formula II, R^{38} is H, -F or fluoro substituted lower alkyl. In certain instances, R^{38} is H, F or CF_3. In another instances, R^{38} is F. In other embodiments, R^{39} is fluoro, chloro, -CN, -OH, $-NH_2$, lower alkoxy, lower alkyl optionally substituted with one or more R^{43},

cycloalkylamino, cycloalkylalkyl-NH-, heterocycloalkylamino and heterocycloalkylalkyl-NH-. In some embodiments, R^{39} is fluoro, chloro, -CN, -OH, $-NH_2$, lower alkyl optionally substituted with fluoro, lower alkoxy, cycloalkylamino, cycloalkylalkyl-NH-, heterocycloalkylamino and heterocycloalkylalkyl-NH-. In a further embodiments, R^{39} is fluoro, chloro, -CN, -OH, $-NH_2$, CH_3, CH_3O-, CF_3, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cyclopropylmethylamino, cyclobutylmethylamino, cyclopentylmethylamino, cyclohexylmethylamino, 2-tetrahydrofuranylamino, 3-tetrahydrofuranylamino or 4-tetrahydropyranylamino. All the other variables are as defined in any of the embodiments of the compounds of Formula II described herein.

[0029] In some embodiments of compounds of Formula II, R^{40} is H, lower alkyl optionally substituted with one or more R^{43}, halogen, lower alkoxy or –CN. In some embodiments, R^{43} is fluoro, -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cycloheptylamino, 2-tetrahydrofuranylamino, 3-tetrahydrofuranylamino, 2-tetrahydropyranylamino, 3-tetrahydropyranylamino or 4-tetrahydropyranylamino. All the other variables are as defined in any of the embodiments of the compounds of Formula II described herein.

[0030] In a third aspect, compounds having the structure according to the following Formula III are provided:



Formula III

or a pharmaceutically acceptable salt thereof,

wherein Y, R^1 and R^2 in Formula III are as defined in any of the embodiments of the compounds of Formula II described herein. In some embodiments:

Y is selected from the group consisting of fluoro, chloro, bromo, iodo, lower alkyl, lower alkoxy, haloalkyl, CN, -OH, fluoro substituted alkyl, cycloalkyl, $-OR^8$, and $-N(R^3)-R^4$;

R^1 is selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, cycloalkyl, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, phenyl optionally substituted with one or more R^6 (e.g., R^1 is 2-fluoro-substituted phenyl, 3-fluoro-substituted phenyl, 2,5-difluoro-substituted phenyl or 4-lower alkyl-substituted phenyl, wherein lower alkyl

is optionally substituted with one or more fluorine), and heteroaryl optionally substituted with one or more R^7;

R^2 is hydrogen, fluoro, chloro, or lower alkyl optionally substituted with one or more fluorine;

R^3 is hydrogen and R^4 is selected from the group consisting of hydrogen, $-OR^8$, lower alkyl optionally substituted with one or more R^{11}, cycloalkyl optionally substituted with one or more R^{12}, heterocycloalkyl optionally substituted with one or more R^{13}, aryl optionally substituted with one or more R^{14}, and heteroaryl optionally substituted with one or more R^{15};

or R^3 and R^4 are both lower alkyl;

or R^3 and R^4 combine with the nitrogen to which they are attached to form cycloalkylamino;

each R^6, when present, is independently selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, $-C(O)-O-R^{18}$, $-N(H)-C(O)-R^{19}$, and heteroaryl optionally substituted with one or more lower alkyl; or two R^6 on adjacent carbons combine to form a fused heterocycloalkyl optionally substituted with one or more lower alkyl;

each R^7, when present, is independently selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, lower alkoxy, $-C(O)-O-R^{20}$, and heteroaryl optionally substituted with one or more lower alkyl;

R^8 is hydrogen, lower alkyl optionally substituted with one or more fluorine, or, when R^8 is a C_{2-6} alkyl, said alkyl may optionally be substituted with one or more R^{21}; cycloalkyl optionally substituted with one or more R^{21}, or heterocycloalkyl optionally substituted with one or more R^{21};

each R^{11}, when present, is independently selected from the group consisting of fluoro, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, cycloalkyl optionally substituted with one or more R^{12}, heterocycloalkyl optionally substituted with one or more R^{13}, aryl optionally substituted with one or more R^{14}, and heteroaryl optionally substituted with one or more R^{15};

each R^{12}, when present, is independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, $-N(H)-C(O)-R^{22}$, $-N(H)-S(O)_2-R^{23}$, $C(O)-R^{24}$, and $S(O)_2-R^{25}$;

each R^{13}, when present, is independently selected from the group consisting of fluoro, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, $-N(H)-C(O)-R^{26}$, $-N(H)-S(O)_2-R^{27}$, $C(O)-R^{28}$, $S(O)_2-R^{29}$, and lower alkyl optionally substituted with one or more R^{30};

each R^{14} and R^{15}, when present, are independently selected from the group consisting of fluoro, chloro, -OH, $-NH_2$, -CN, $-NO_2$, $-N(H)-C(O)-R^{31}$, $-N(H)-S(O)_2-R^{32}$, $C(O)-R^{33}$, $S(O)_2-R^{34}$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, aryl optionally substituted with one or more R^{35}, and heteroaryl optionally substituted with one or more R^{36};

each R^{17}, when present, is independently fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{18} and R^{20}, when present, are independently hydrogen, lower alkyl or fluoro substituted lower alkyl;

each R^{19}, R^{22}, R^{23}, R^{26}, R^{27}, R^{31} and R^{32}, when present, are independently lower alkyl, fluoro substituted lower alkyl, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{21}, when present, is fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{24}, R^{25}, R^{28}, R^{29}, R^{33}, and R^{34}, when present, are independently lower alkyl, fluoro substuted lower alkyl, -OH, lower alkoxy, fluor substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, , or heterocycloalkylamino;

each R^{30}, when present, is independently fluoro, aryl optionally substituted with one or more R^{35} or heteroaryl optionally substituted with one or more R^{36}; and

each R^{35} and R^{36}, when present, are independently selected from the group consisting of fluoro, chloro, -OH, $-NH_2$, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino.

[0031] In some embodiments of compounds of Formula III, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like. In some embodiments of compounds of Formula III, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl , i-propyl, sec-butyl, i-butyl, and the like; and R^2 is hydrogen. In some embodiments of compounds of Formula III, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl , i-propyl, sec-butyl, i-butyl, and the like; and R^2 is fluoro. In some embodiments, R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like. All the other variables are as defined in any of the embodiments of the compounds of Formulas I, II and III described herein.

[0032] In some embodiments of compounds of Formula III, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like. In some embodiments of compounds of Formula III, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like; and R^2 is hydrogen. In some embodiments of compounds of Formula III, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like; and R^2 is fluoro. In some embodiments, R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like. All the other variables are as defined in any of the embodiments of the compounds of Formulas I, II and III described herein.

[0033] In some embodiments of compounds of Formula III, Y is $-OR^8$; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like. In some embodiments of compounds of Formula III, Y is $-OR^8$; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like; and R^2 is hydrogen. In some embodiments of compounds of Formula III, Y is $-OR^8$; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like; and R^2 is fluoro. In some embodiments, R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like, and R^8 is hydrogen or lower alkyl. All the other variables are as defined in any of the embodiments of the compounds of Formulas I, II and III described herein.

[0034] In some embodiments of compounds of Formula III, $Y–N(R^3)-R^4$; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like. In some embodiments of compounds of Formula III, $Y–N(R^3)-R^4$; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like; and R^2 is hydrogen. In some embodiments of compounds of Formula III, $Y–N(R^3)-R^4$; R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like; and R^2 is fluoro. In some embodiments, R^1 is lower alkyl or cycloalkyl, preferably lower alkyl, preferably n-propyl, i-propyl, sec-butyl, i-butyl, and the like, R^3 is hydrogen and R^4 is selected from the group consisting of hydrogen, -OH, lower alkyl optionally substituted with R^{11}, cycloalkyl, heterocycloalkyl optionally substituted with lower alkyl, phenyl optionally substituted with one or more R^{14}, and 5-6 membered heteroaryl optionally substituted with one or more lower alkyl, or R^3 and R^4 are both lower alkyl, or R^3 and R^4 combine with the nitrogen to which they are attached to form cycloalkylamino, wherein R^{11} and R^{14} are as defined for Formula I, preferably wherein R^{11} is selected from the group consisting of cycloalkyl, -OH, lower alkoxy,

mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino, and R^{14} is selected from the group consisting of fluoro, chloro, -CN, -NO_2, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. All the other variables are as defined in any of the embodiments of the compounds of Formulas I, II and III described herein.

[0035] In some embodiments of compounds of Formula III, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino. In some embodiments of compounds of Formula III, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino; and R^2 is hydrogen. In some embodiments of compounds of Formula III, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino; and R^2 is fluoro. In some embodiments, R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino. All the other variables are as defined in any of the embodiments of the compounds of Formulas I, II and III described herein.

[0036] In some embodiments of compounds of Formula III, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino. In some embodiments of compounds of Formula III, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino; and R^2 is hydrogen. In some embodiments of compounds of Formula III, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino; and R^2 is fluoro. In some embodiments, R^1 is mono-alkylamino, di-alkylamino, or cycloalkylamino, preferably di-alkylamino, cycloalkylamino, or heterocycloalkylamino. All the other variables are as defined in any of the embodiments of the compounds of Formulas I, II and III described herein.

[0037] In some embodiments of compounds of Formula III, Y is -OR^8; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino. In some embodiments of compounds of Formula III, Y is -OR^8; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino; and R^2 is hydrogen. In some embodiments of compounds of Formula III, Y is -OR^8; R^1 is mono-alkylamino,

di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino; and R^2 is fluoro. In some embodiments, R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino, and R^8 is hydrogen or lower alkyl. All the other variables are as defined in any of the embodiments of the compounds of Formulas I, II and III described herein.

[0038] In some embodiments of compounds of Formula III, Y is–$N(R^3)$-R^4; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino. In some embodiments of compounds of Formula III, Y is–$N(R^3)$-R^4; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino; and R^2 is hydrogen. In some embodiments of compounds of Formula III, Y is–$N(R^3)$-R^4; R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino; and R^2 is fluoro. In some embodiments, R^1 is mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino, preferably di-alkylamino or cycloalkylamino, R^3 is hydrogen and R^4 is selected from the group consisting of hydrogen, -OH, lower alkyl optionally substituted with R^{11}, cycloalkyl, heterocycloalkyl optionally substituted with lower alkyl, phenyl optionally substituted with one or more R^{14}, and 5-6 membered heteroaryl optionally substituted with one or more lower alkyl, or R^3 and R^4 are both lower alkyl, or R^3 and R^4 combine with the nitrogen to which they are attached to form cycloalkylamino, wherein R^{11} and R^{14} are as defined for Formula I, preferably wherein R^{11} is selected from the group consisting of cycloalkyl, -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino, and R^{14} is selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. All the other variables are as defined in any of the embodiments of the compounds of Formulas I, II and III described herein.

[0039] In some embodiments of compounds of Formula III, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. In some embodiments of compounds of Formula III, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and R^2 is hydrogen. In some embodiments of compounds of Formula III, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower

alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and R^2 is fluoro. In some embodiments, R^1 is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy. In some embodiments, R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. All the other variables are as defined in any of the embodiments of the compounds of Formulas I, II and III described herein.

[0040] In some embodiments of compounds of Formula III, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. In some embodiments of compounds of Formula III, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and R^2 is hydrogen. In some embodiments of compounds of Formula III, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and R^2 is fluoro. In some embodiments, R^1 is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy. In some embodiments, R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. All the other variables are as defined in any of the embodiments of the compounds of Formulas I, II and III described herein.

[0041] In some embodiments of compounds of Formula III, Y is $-OR^8$; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. In some embodiments, R^1 is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy. In some embodiments of compounds of Formula III, Y is $-OR^8$; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. In some embodiments, R^1 is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy. In some

embodiments of compounds of Formula III, Y is $-OR^8$; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and R^2 is hydrogen. In some embodiments, R^1 is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy; and R^2 is fluoro. In some embodiments, R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy, and R^8 is hydrogen or lower alkyl. All the other variables are as defined in any of the embodiments of the compounds of Formulas I, II and III described herein.

[0042] In some embodiments of compounds of Formula III, Y is $-N(R^3)-R^4$; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. In some embodiments of compounds of Formula III, Y is $-N(R^3)-R^4$; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and R^2 is hydrogen. In some embodiments of compounds of Formula III, Y is $-N(R^3)-R^4$; R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and R^2 is fluoro. In some embodiments, R^1 is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy. In some embodiments, R^1 is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy, R^3 is hydrogen and R^4 is selected from the group consisting of hydrogen, -OH, lower alkyl optionally substituted with R^{11}, cycloalkyl, heterocycloalkyl optionally substituted with lower alkyl, phenyl optionally substituted with one or more R^{14}, and 5-6 membered heteroaryl optionally substituted with one or more lower alkyl, or R^3 and R^4 are both lower alkyl, or R^3 and R^4 combine with the nitrogen to which they are attached to form cycloalkylamino wherein R^{11} and R^{14} are as defined for Formula I, preferably wherein R^{11} is selected from the group consisting of cycloalkyl, -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino , and heterocycloalkylamino, and R^{13} is selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. In some embodiments, R^1 is phenyl mono-substituted with fluoro, lower alkyl, or $-CF_3$, or di-substitited with two fluoro, two lower alkyl, or one fluoro and one lower alkoxy, R^3 is hydrogen and R^4 is selected from the group consisting of hydrogen, -OH, lower alkyl optionally substituted with R^{11},

cycloalkyl, heterocycloalkyl optionally substituted with lower alkyl, phenyl optionally substituted with one or more R^{14}, and 5-6 membered heteroaryl optionally substituted with one or more lower alkyl, or R^3 and R^4 are both lower alkyl, or R^3 and R^4 combine with the nitrogen to which they are attached to form cycloalkylamino, wherein R^{11} and R^{14} are as defined for Formula I, preferably wherein R^{11} is selected from the group consisting of cycloalkyl, -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino, and R^{14} is selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. All the other variables are as defined in any of the embodiments of the compounds of Formulas I, II and III described herein.

[0043] In some embodiments of compounds of Formula III, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy. In some embodiments of compounds of Formula III, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is hydrogen. In some embodiments of compounds of Formula III, Y is fluoro, chloro, bromo, or iodo, preferably fluoro; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is fluoro. In some embodiments, R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy. All the other variables are as defined in any of the embodiments of the compounds of Formulas I, II and III described herein.

[0044] In some embodiments of compounds of Formula III, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy. In some embodiments of compounds of Formula III, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is hydrogen. In some embodiments of compounds of Formula III, Y is lower alkyl, fluoro substituted alkyl, or cycloalkyl; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower

alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is fluoro. In some embodiments, R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy. All the other variables are as defined in any of the embodiments of the compounds of FormulasI, II and III described herein.

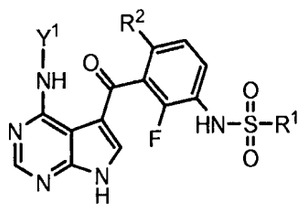
[0045] In some embodiments of compounds of Formula III, Y is $-OR^8$; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy. In some embodiments of compounds of Formula III, Y is $-OR^8$; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is hydrogen. In some embodiments of compounds of Formula III, Y is $-OR^8$; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is fluoro. In some embodiments, R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy, and R^8 is hydrogen or lower alkyl. All the other variables are as defined in any of the embodiments of the compounds of Formulas I, II and III described herein.

[0046] In some embodiments of compounds of Formula III, Y is $-N(R^3)-R^4$; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy. In some embodiments of compounds of Formula III, Y is $-N(R^3)-R^4$; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is hydrogen. In some embodiments of compounds of Formula III, Y is $-N(R^3)-R^4$; R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy; and R^2 is fluoro. In some embodiments, R^1 is 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower alkyl and lower alkoxy, preferably pyrdinyl mono- or di-substituted with methoxy, R^3 is hydrogen and R^4 is selected from the group consisting of hydrogen, -OH, lower alkyl optionally substituted with R^{11}, cycloalkyl, heterocycloalkyl optionally substituted with lower alkyl, phenyl optionally substituted with one or more R^{14}, and 5-6 membered heteroaryl optionally

substituted with one or more lower alkyl, or R^3 and R^4 are both lower alkyl, or R^3 and R^4 combine with the nitrogen to which they are attached to form cycloalkylamino, wherein R^{11} and R^{14} are as defined for Formula I, preferably wherein R^{11} is selected from the group consisting of cycloalkyl, -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino, and R^{14} is selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. All the other variables are as defined in any of the embodiments of the compounds of Formulas I, II and III described herein.

[0047] In some embodiments of compounds of Formulas I, II and III, Y is fluoro, chloro, bromo, iodo, lower alkyl, lower alkoxy, haloalkyl, CN, -OH, cycloalkyl, $-OR^8$ or $-NH(R^4)$. In a preferred embodiment, Y is CH_3, ethyl, methoxy, ethyoxy, isobutyl, CN, OH, F, Cl, Br, I, NH_2, butyoxy, 2-methylpropoxy, 4-tetrahydropyranyloxy, 2-tetrahyrofuranyloxy, 3-tetrahyrofuranyloxy, alkoxyamino or HO-NH-.

[0048] In another aspects, the invention provides a compound having subformula IIIa:



IIIa

wherein Y^1 is lower alkyl optionally substituted with from one to three R^{11}, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, wherein:
the cycloalkyl and cycloalkylalkyl are each optionally substituted with from one to three R^{12};
the heterocycloalkyl and heterocycloalkylalkyl are each optionally substituted with from one to three R^{13};
the aryl and arylalkyl are each optionally substituted with from one to three R^{14} optionally, wherein the two adjacent R^{14} groups on the aryl ring are taken together to form a 5 or 6-membered hetero aromatic ring having from 1-4 heteroatoms selected from O or N; and the heteroaryl and heteroarylalkyl are each optionally substituted with from one to three R^{15}. The other variables R^1 and R^2 are as defined in any of the embodiments of compounds of Formulas I, II and III described herein.

[0049] In some embodiments of the compounds of Formula IIIa, Y^1 is selected from lower alkyl, halogen substituted lower alkyl, 2-hydroxyethyl, cyclopropylamino, cyclobutyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexyl, 2-oxetanyl, 2-oxetanylmethyl, 3-oxetanyl, 3-oxetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-

tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 2-tetrahydropyranylmethyl, 3-tetrahydropyranylmethyl, 4-tetrahydropyranylmethyl, 1-methyl-2-aziridinyl, 1-methyl-2-aziridinylmethyl, 1-methyl-2-azetidinyl, 1-methyl-2-azetidinylmethyl, 1-methyl-3-azetidinyl, 1-methyl-3-azetidinylmethyl, 1-methyl-2-pyrrolidinyl, 1-methyl-2-pyrrolidinylmethyl, 1-methyl-3-pyrrolidinyl, 1-methyl-3-pyrrolidinylmethyl, 1-methyl-2-piperidinyl, 1-methyl-2-piperidinylmethyl, 1-methyl-3-piperidinyl, 1-methyl-3-piperidinylmethyl, 1-methyl-4-piperidinyl, 1-methyl-4-piperidinylmethyl, 1-methylsulfonyl-2-piperidinyl, 1-methylsulfonyl-2-piperidinylmethyl, 1-methylsulfonyl-3-piperidinyl, 1-methylsulfonyl-3-piperidinylmethyl, 1-methylsulfonyl-4-piperidinyl, 1-methylsulfonyl-4-piperidinylmethyl, 1,1-dioxo-4-thianyl, 1,1-dioxo-4-thianylmethyl, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-benzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-pyridyl, 2-pyridylmethyl, 3-pyridyl, 3-pyridylmethyl, 4-pyridyl, 4-pyridylmethyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-dimethylaminophenyl, 3-dimethylaminophenyl, 4-dimethylaminophenyl, 2-dimethylaminobenzyl, 2-dimethylaminobenzyl, 3-dimethylaminobenzyl, 4-dimethylaminobenzyl, 2-hydoxyphenyl, 3-hydoxyphenyl, 4-hydoxyphenyl, 2-hydroxybenzyl, 3-hydroxybenzyl, 4-hydroxybenzyl, 2-carboxyphenyl, 3-carboxyphenyl, 4-carboxyphenyl, 2-carboxybenzyl, 3-carboxybenzyl, 4-carboxybenzyl, 2-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methoxycarbonylphenyl, 2-methoxycarbonylbenzyl, 3-methoxycarbonylbenzyl, 4-methoxycarbonylbenzyl, 1-alkyl-4-pyrazolyl, 1-alkyl-4-pyrazolylmethyl, 3-pyridazinyl, pyridazinylmethyl, 4-pyridazinyl, 4-pyridazinylmethyl, triazolyl, triazolymethyl, tetrazolyl, tetrazolymethyl, 2,1,3,-benzoxadiazolyl, 2,1,3-benzoxadiazol-5-yl, 2,1,3,-benzoxadiazolyl-methyl, 2,1,3-benzoxadiazol-5ylmethyl, 2,1,3,-benzothiadiazolyl, 2,1,3-benzothiadiazol-5-yl, 2,1,3,-benzothiadiazolyl-methyl, 2,1,3-benzothiadiazol-5ylmethyl, 1H-1,2,4-triazol-5-yl, 1H-1,2,4-triazol-5-methyl, 2-oxobenzimidazol-4-yl, 2-oxobenzimidazol-4-methyl, 2-oxobenzimidazol-5-yl, 2-oxobenzimidazol-5-methyl, 1,1,-dioxo-thiolan-3-yl, 1,1-dioxothiolan-3-methyl, 3-(2-methyl-1,2,3,4-tetrazol-5-yl)phenyl, 3-(2-methyl-1,2,3,4-tetrazol-5-yl)benzyl, 3-(5-methyl-1,2,3,4-tetrazol-1-yl)phenyl, 3-(1,2,4-triazol-5-yl)phenyl, 3-(1,2,,4-triazol-5-yl)benzyl, 3-3-methyl-4H-1,2,4-triazol-5-methyl or 2-(3-methyl-4H-1,2,4-triazol-5-yl)ethyl. In certain instances, Y^1 is cyclopropylmethyl. The other variables R^1 and R^2 are as defined in any of the embodiments of compounds of Formulas I, II, III and IIIa described herein.

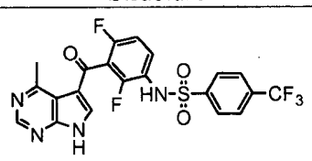
[0050] In some embodiments of the compounds of Formula IIIa, R^2 is H or F. The other variables R^1 and Y^1 are as defined in any of the embodiments of compounds of Formulas I, II, III and IIIa described herein.

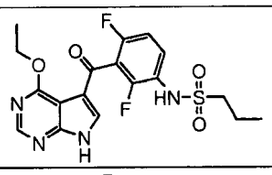
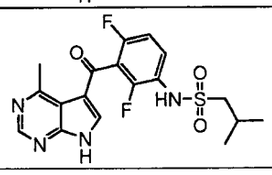
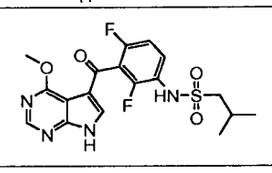
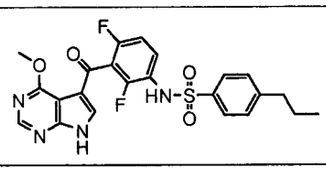
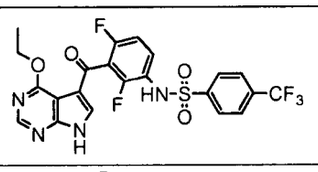
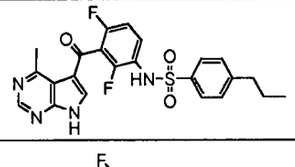
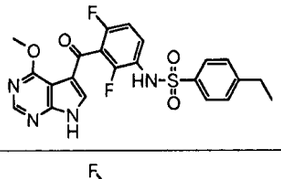
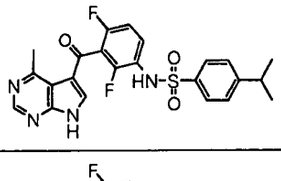
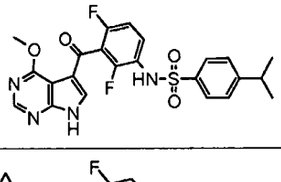
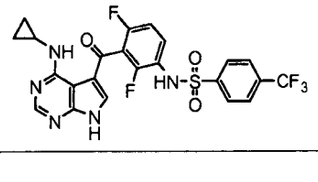
[0051] In some embodiments of the compounds of Formulas I, II, III and IIIa, R^1 is lower alkyl, cycloalkyl optionally substituted with 1-2 groups selected from halogen or lower alkyl, heterocycloalkyl, heteroaryl optionally substituted with lower alkyl or lower alkoxy, phenyl optionally substituted with 1-2 substitutents selected from lower alkyl, halogen, lower alkoxy, haloalkyl, haloalkoxy or CN. In some embodiments, R^1 is methyl, propyl, isobutyl, 2-methylpropyl, CF_3, CF_3CH_2-, CHF_2CH_2-, 4-trifluorophenyl, 2-trifluorophenyl, 3-trifluorophenyl, 3,5-dimethylphenyl, 4-propylphenyl, 3-fluoro-4-methoxyphenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-fluoro-3-methoxyphenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,4-difluorophenyl, 2-pyridyl, 3-pyridyl, 5-methoxy-2-pyridyl, 3-methoxy-2-pyridyl, 4-methoxy-2-pyridyl, 6-methyl-2-pyridyl, 5-methyl-2-pyridyl, 4-methyl-2-pyridyl, 3-methyl-2-pyridyl, dialkylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, cycloprpyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-difluorocyclohexyl, 1-methyl-4-pyrazolyl, 1-ethyl-4-pyrazolyl, 1-methyl-3-pyrazolyl, 1-ethyl-3-pyrazolyl, 6-methyl-3-pyridyl, 5-methyl-3-pyridyl, 4-methyl-3-pyridyl or 2-methyl-3-pyridyl. In a further embodiment, R^1 is 2-fluorophenyl, 3-fluorophenyl, 2,5-difluorophenyl or 4-lower alkyl-substituted phenyl, wherein lower alkyl is optionally substituted with one or more fluorine. All the other variables are as defined in any of the embodiments of compounds of Formulas I, II, III and IIIa described herein.

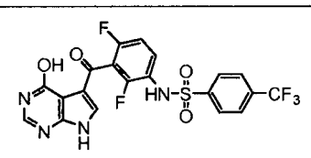
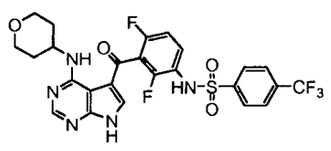
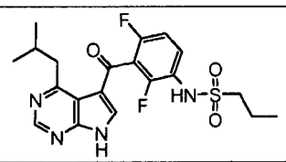
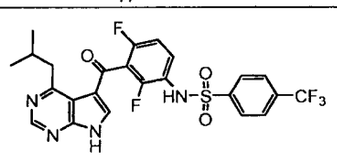
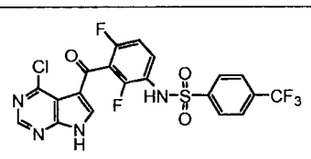
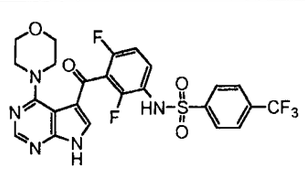
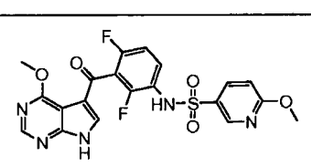
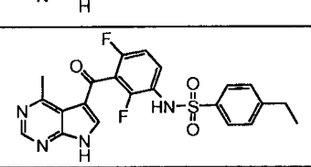
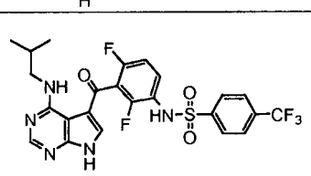
[0052] In a particular group of embodiments of compounds of Formulas I, II, III and IIIa, Y is $-NR^3R^4$, wherein R^3 and R^4 combine with the nitrogen atom to which they are attached to form a three to seven membered ring having 0-1 additional ring heteroatom selected from O, N or S, wherein the nitrogen or sulfur atom is optionally oxidized. In certain instances, Y is 1-aziridinyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl or 1-azepanyl. All the other variables are as defined in any of the embodiments of compounds of Formulas I, II, III and IIIa described herein.

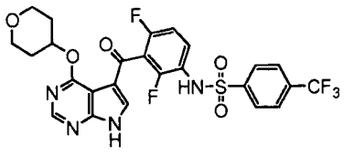
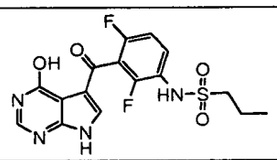
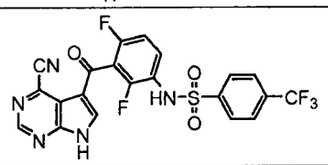
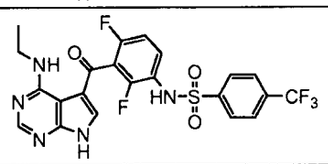
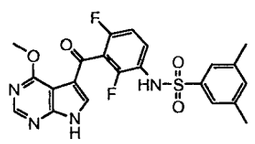
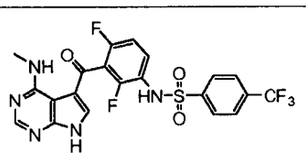
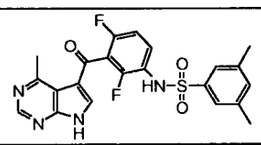
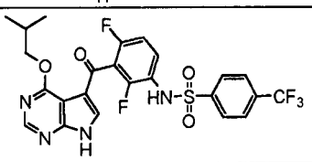
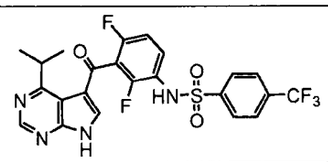
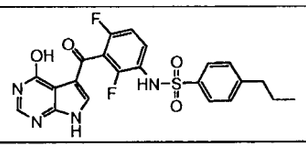
[0053] In various aspects and embodiments, provided are the compounds shown in Table I below, and/or pharmaceutically acceptable salts of the compounds shown in Table I.

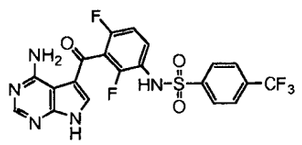
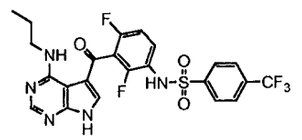
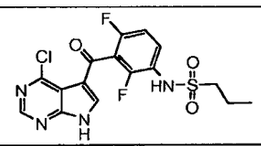
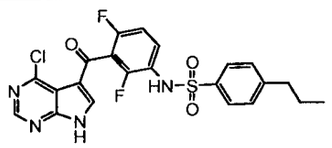
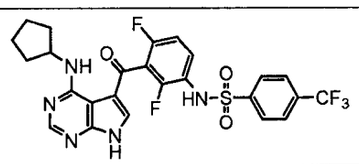
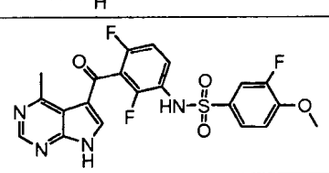
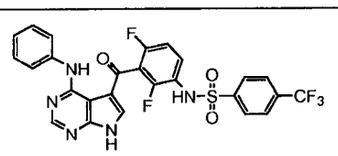
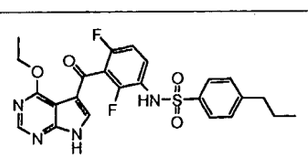
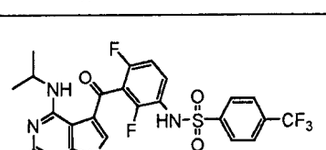
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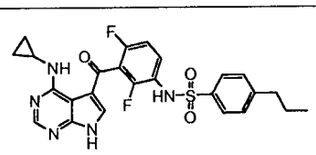
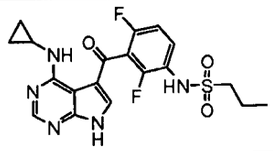
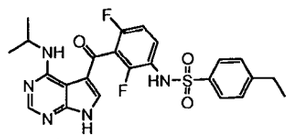
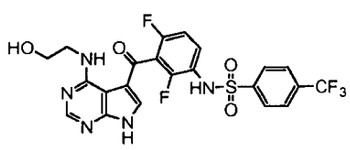
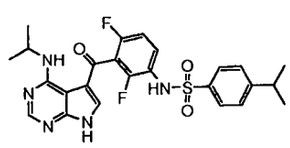
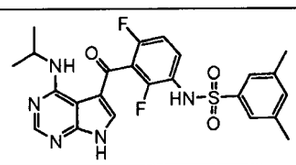
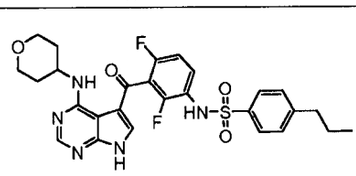
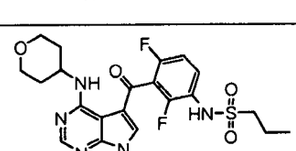
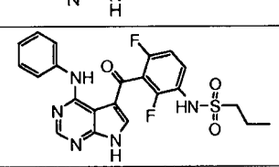
Comp #	Structure	Name	MS
P-1001		N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide	496.9

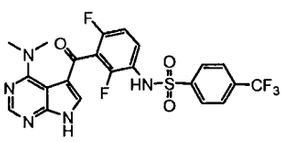
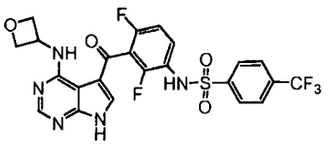
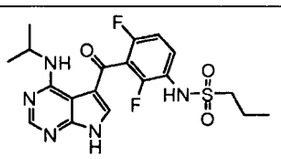
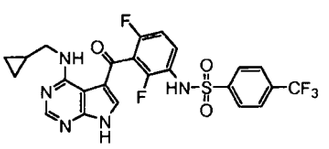
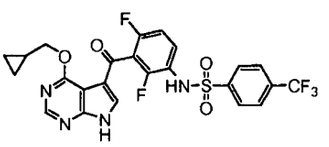
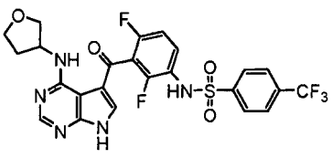
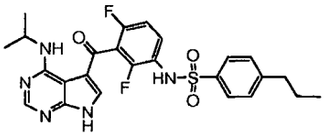
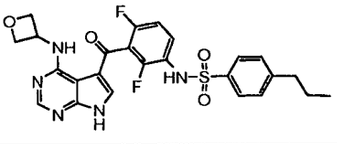
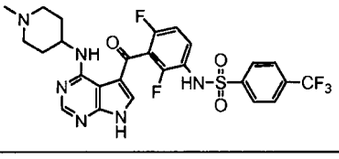
P-1002		Propane-1-sulfonic acid [3-(4-ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide	424.9
P-1003		2-Methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	409.3
P-1004		2-Methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	425.1
P-1005		N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide	486.95
P-1006.		N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide	526.95
P-1007		N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide	470.95
P-1008		N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide	473.0
P-1009		N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide	471.3
P-1010		N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide	486.8
P-1011		N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide	537.8

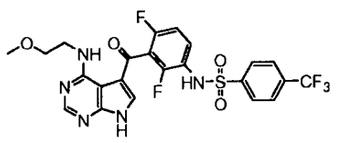
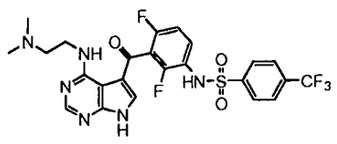
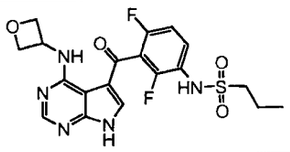
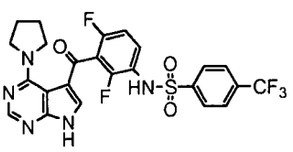
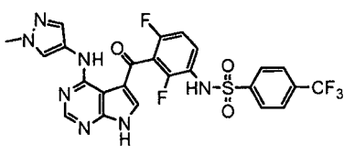
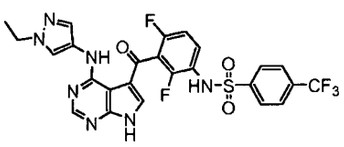
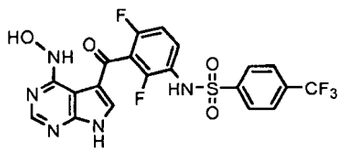
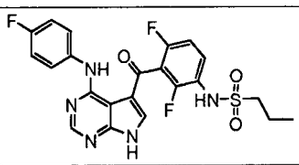
P-1012		N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide	499.0
P-1013		N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide	581.8; 582.0
P-1014		Propane-1-sulfonic acid [2,4-difluoro-3-(4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	436.7
P-1015		N-[2,4-Difluoro-3-(4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide	538.6
P-1016		N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide	516.9
P-1017		N-[2,4-Difluoro-3-(4-morpholin-4-yl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide	567.8
P-1018		6-Methoxy-pyridine-3-sulfonic acid [2,4-difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	476.0
P-1019		N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide	457.2
P-1020		N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide	554.4; 554.0

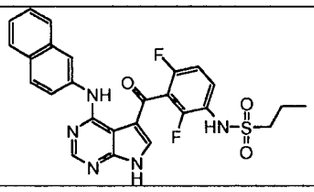
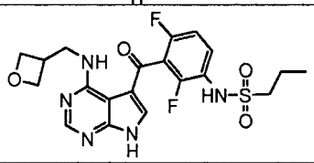
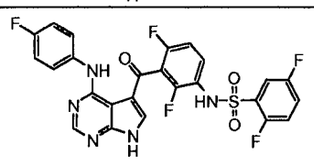
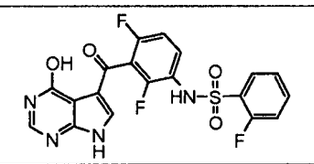
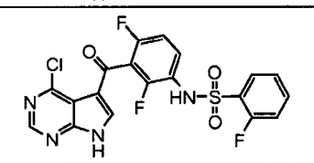
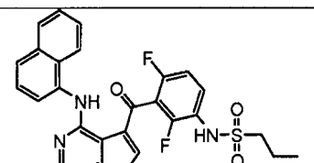
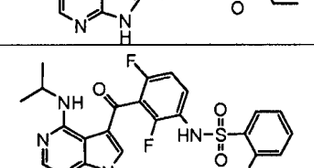
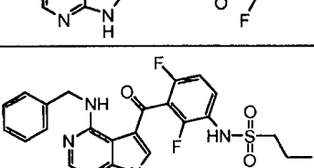
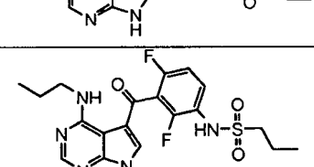
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P-1022		Propane-1-sulfonic acid [2,4-difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	397.0
P-1023		N-[3-(4-Cyano-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide	508.1
P-1024		N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide	525.95
P-1025		N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3,5-dimethyl-benzenesulfonamide	473.0
P-1026		N-[2,4-Difluoro-3-(4-methylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide	512.0
P-1027		N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3,5-dimethyl-benzenesulfonamide	456.95
P-1028		N-[2,4-Difluoro-3-(4-isobutoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide	553.2
P-1029		N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide	525.2
P-1030		N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-	472.9

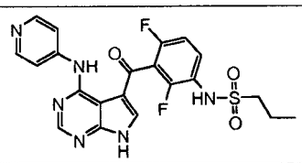
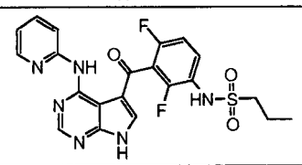
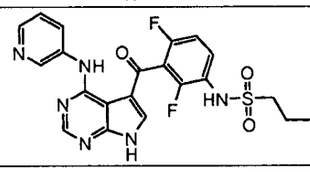
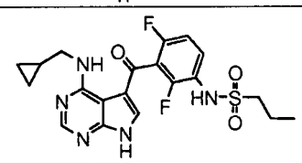
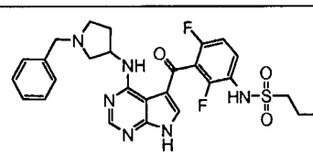
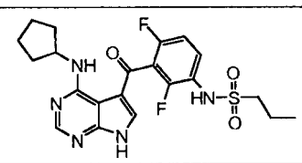
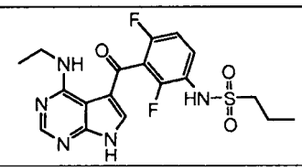
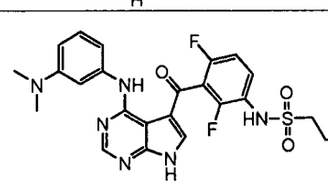
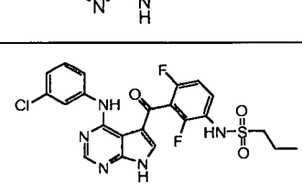
		benzenesulfonamide	
P-1031		N-[3-(4-Amino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide	497.9
P-1032		N-[2,4-Difluoro-3-(4-propylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide	539.95
P-1033		Propane-1-sulfonic acid [3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide	414.8
P-1034		N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide	490.9
P-1035		N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide	566.3
P-1036		N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-fluoro-4-methoxy-benzenesulfonamide	477.0
P-1037		N-[2,4-Difluoro-3-(4-phenylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide	573.9
P-1038		N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide	501.0
P-1039		N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide	540.0

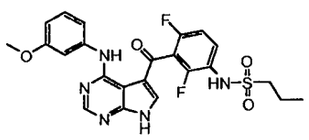
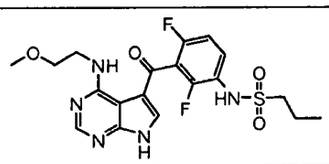
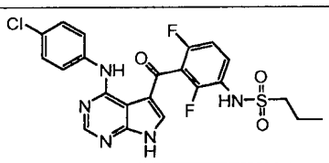
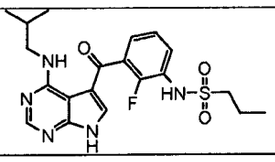
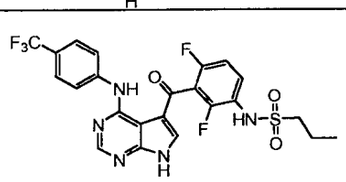
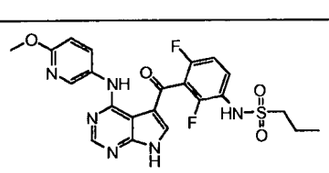
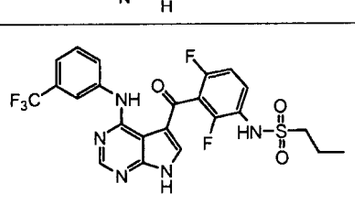
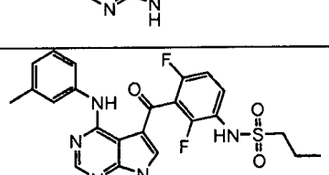
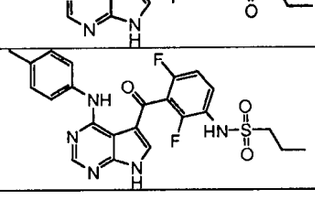
P-1040		N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide	512.0
P-1041		Propane-1-sulfonic acid [3-(4-cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide	435.95
P-1042		N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide	500.27
P-1043		N-{2,4-Difluoro-3-[4-(2-hydroxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide	541.95
P-1044		N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide	514.0
P-1045		N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3,5-dimethyl-benzenesulfonamide	500.05
P-1046		N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-propyl-benzenesulfonamide	556.0
P-1047		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	479.95
P-1048		Propane-1-sulfonic acid [2,4-difluoro-3-(4-phenylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	473.95

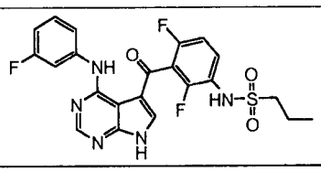
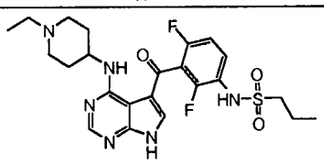
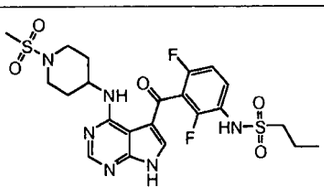
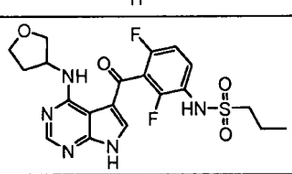
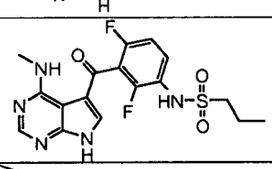
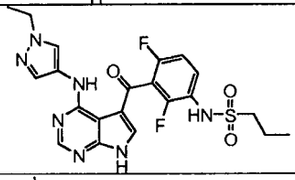
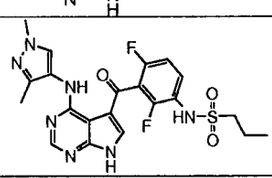
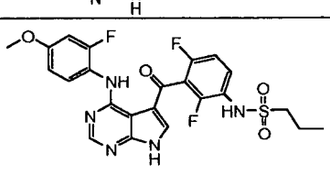
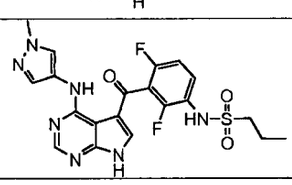
P-1049		N-[3-(4-Dimethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide	525.95
P-1050		N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide	554.0
P-1051		Propane-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	437.95
P-1052		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide	552.2
P-1053		N-[3-(4-Cyclopropylmethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide	553.2
P-1054		N-{2,4-Difluoro-3-[4-(tetrahydro-furan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide	568.0
P-1055		N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide	514.0
P-1056		N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-propyl-benzenesulfonamide	528.0
P-1057		N-{2,4-Difluoro-3-[4-(1-methyl-piperidin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-	595.0

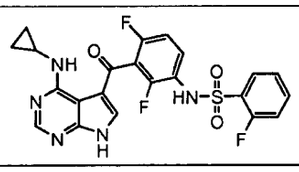
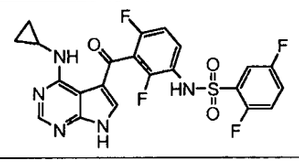
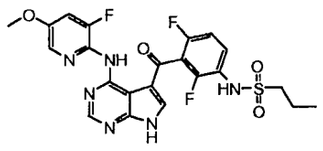
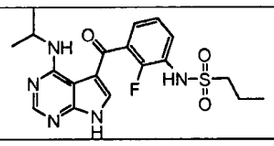
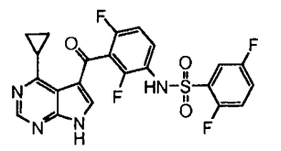
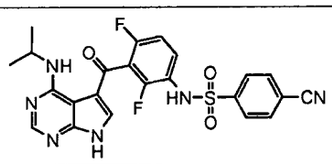
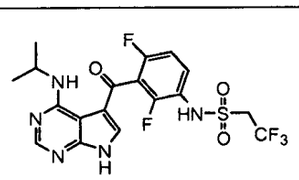
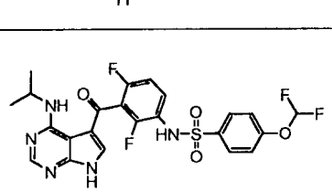
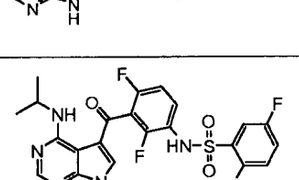
		benzenesulfonamide	
P-1058		N-{2,4-Difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide	556.3
P-1059		N-{3-[4-(2-Dimethylamino-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide	569.5
P-1060		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	451.95
P-1061		N-[2,4-Difluoro-3-(4-pyrrolidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide	552.5
P-1062		N-{2,4-Difluoro-3-[4-(1-methyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide	578.1
P-1063		N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide	592.5
P-1064		N-[2,4-Difluoro-3-(4-hydroxyamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide	513.9
P-1065		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(4-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	490.0

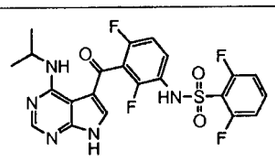
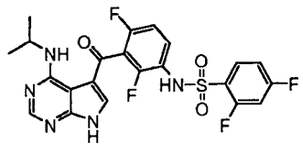
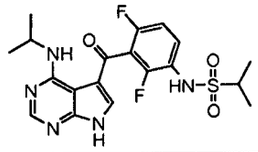
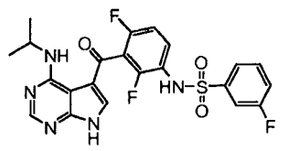
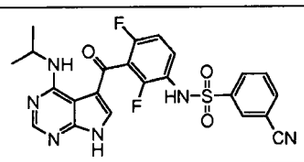
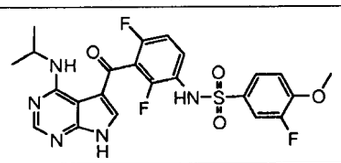
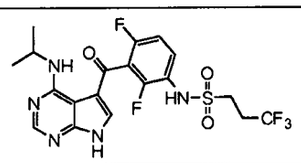
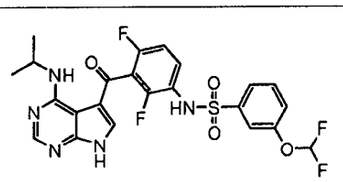
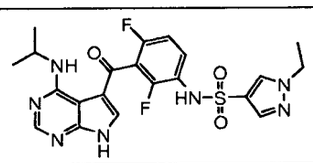
P-1067		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(naphthalen-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	522.25
P-1068		Propane-1-sulfonic acid (2,4-difluoro-3-{4-[(oxetan-3-ylmethyl)-amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide	513.9
P-1069		N-{2,4-Difluoro-3-[4-(4-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide	559.9
P-1070		N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide	448.9
P-1071		N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide	466.9/ 468.9
P-1072		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(naphthalen-1-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	522.0
P-1073		N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide	490.0
P-1074		Propane-1-sulfonic acid [3-(4-benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide	486.5
P-1075		Propane-1-sulfonic acid [2,4-difluoro-3-(4-propylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	438.0

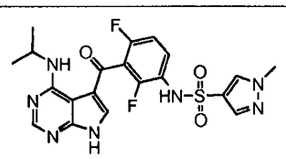
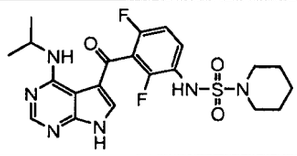
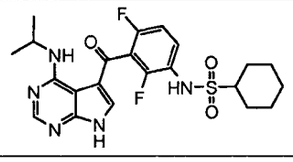
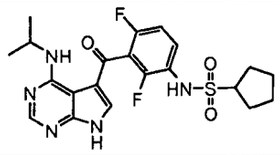
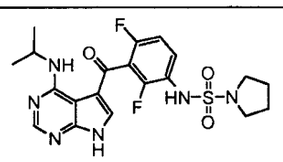
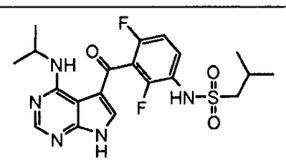
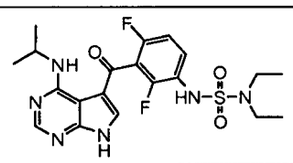
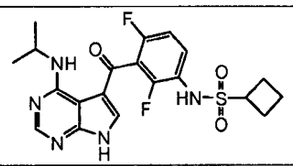
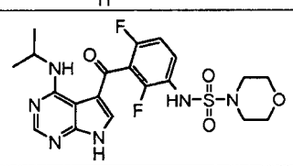
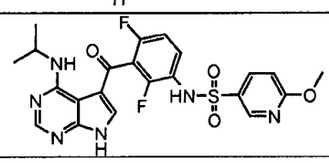
P-1076		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(pyridin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	473.0
P-1077		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	473.0
P-1078		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	473.0
P-1079		Propane-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	450.0
P-1080		Propane-1-sulfonic acid {3-[4-(1-benzyl-pyrrolidin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	555.5
P-1081		Propane-1-sulfonic acid [3-(4-cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide	464.0
P-1082		Propane-1-sulfonic acid [3-(4-ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide	424.0
P-1083		Propane-1-sulfonic acid {3-[4-(3-dimethylamino-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	515.5
P-1084		Propane-1-sulfonic acid {3-[4-(3-chloro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	506.0

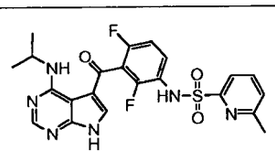
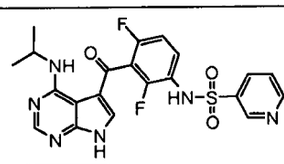
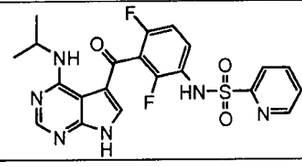
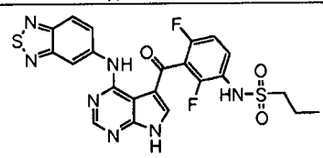
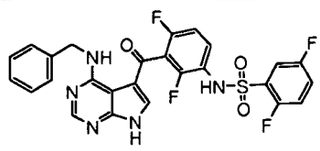
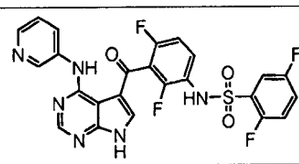
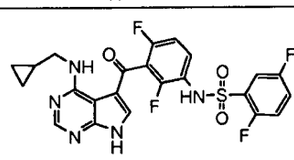
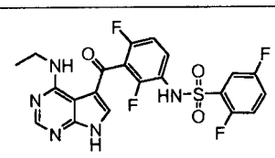
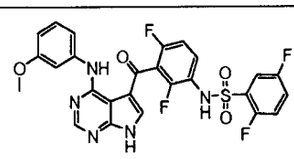
P-1085		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	502.5
P-1086		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	454.0
P-1087		Propane-1-sulfonic acid {3-[4-(4-chloro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	506.0
P-1088		Propane-1-sulfonic acid [2,4-difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	452.0
P-1089		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(4-trifluoromethyl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	540.5
P-1090		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(6-methoxy-pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	503.0
P-1091		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-trifluoromethyl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	540.5
P-1092		Propane-1-sulfonic acid [2,4-difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	486.5
P-1093		Propane-1-sulfonic acid [2,4-difluoro-3-(4-p-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	486.5

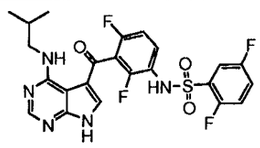
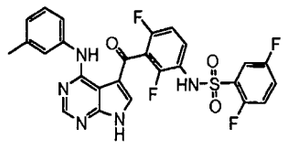
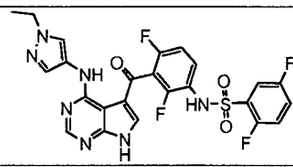
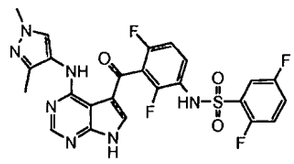
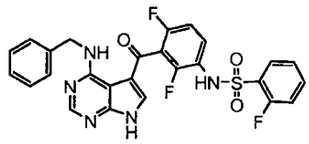
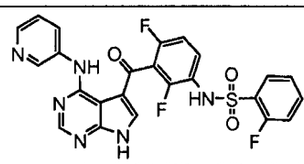
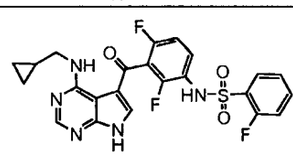
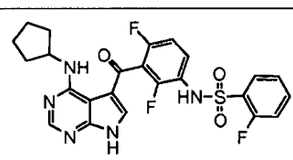
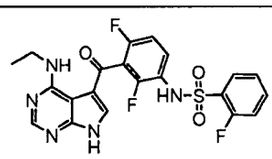
P-1094		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	490.5
P-1095		Propane-1-sulfonic acid {3-[4-(1-ethyl-piperidin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	507.5
P-1096		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1-methanesulfonyl-piperidin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	557.5
P-1097		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(tetrahydro-furan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	466.5
P-1098		Propane-1-sulfonic acid [2,4-difluoro-3-(4-methylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	410.0
P-1099		Propane-1-sulfonic acid {3-[4-(1-ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	490.5
P-1100		Propane-1-sulfonic acid {3-[4-(1,3-dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	490.5
P-1101		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(2-fluoro-4-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	520.5
P-1102		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1-methyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	476.0

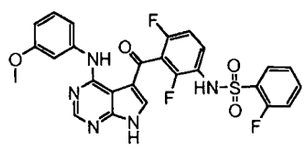
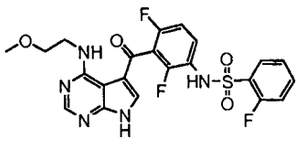
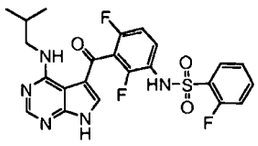
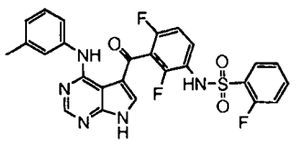
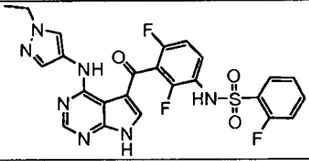
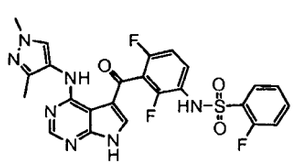
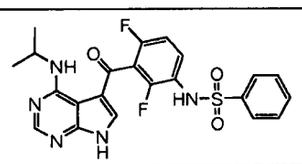
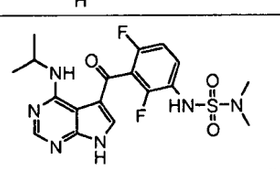
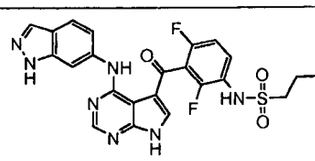
P-1103		N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide	488.0
P-1104		N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide	506.0
P-1105		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-fluoro-5-methoxy-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	521.0
P-1106		Propane-1-sulfonic acid [2-fluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	420.0
P-1107		N-[3-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide	491.4
P-1108		4-Cyano-N-[2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-benzenesulfonamide	497.5
P-1109		2,2,2-Trifluoro-ethanesulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	478.0
P-1110		N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-difluoromethoxy-benzenesulfonamide	538.5
P-1111		N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide	508.0

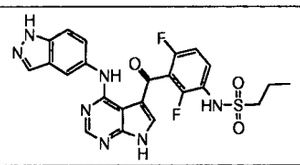
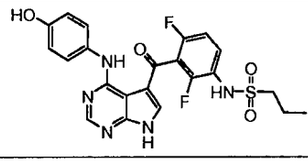
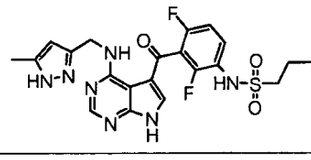
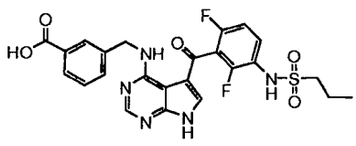
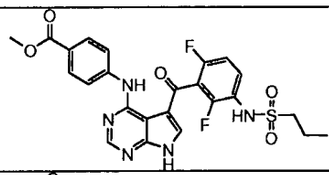
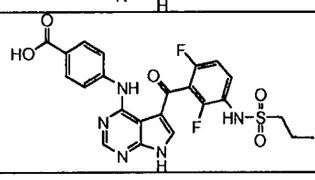
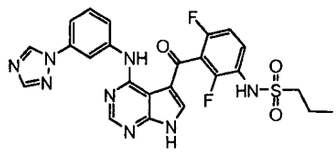
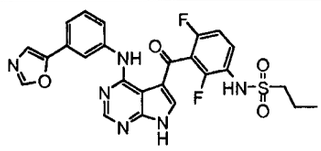
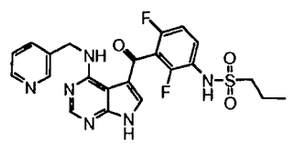
P-1112		N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,6-difluoro-benzenesulfonamide	508.0
P-1113		N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,4-difluoro-benzenesulfonamide	508.0
P-1114		Propane-2-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	438.0
P-1115		N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-fluoro-benzenesulfonamide	490.5
P-1116		3-Cyano-N-[2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-benzenesulfonamide	497.5
P-1117		N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-fluoro-4-methoxy-benzenesulfonamide	520.5
P-1118		3,3,3-Trifluoro-propane-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	492.0
P-1119		N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-difluoromethoxy-benzenesulfonamide	538.5
P-1120		1-Ethyl-1H-pyrazole-4-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	490.5

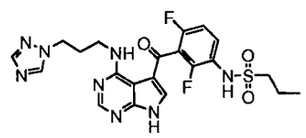
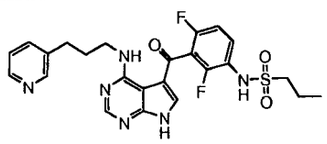
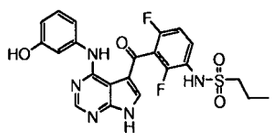
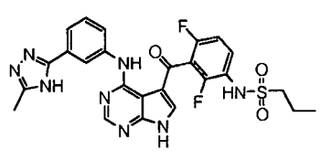
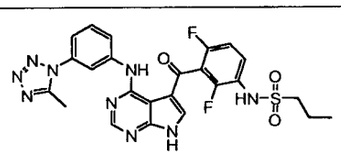
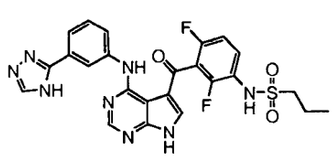
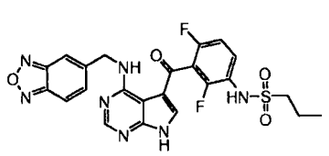
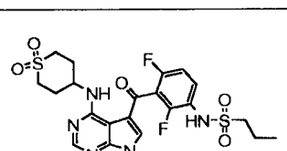
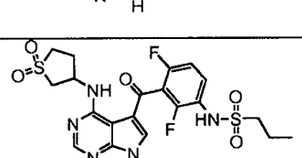
P-1121		1-Methyl-1H-pyrazole-4-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	476.0
P-1122		Piperidine-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	479.0
P-1123		Cyclohexanesulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	478.0
P-1124		Cyclopentanesulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	464.0
P-1125		Pyrrolidine-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	465.0
P-1126		2-Methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	452.0
P-1127		Diethylamine-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	467.5
P-1128		Cyclobutanesulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	450.0
P-1129		Morpholine-4-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	481.0
P-1130		6-Methoxy-pyridine-3-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-	503.0

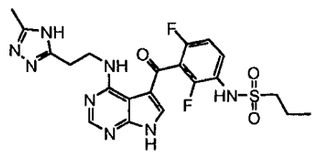
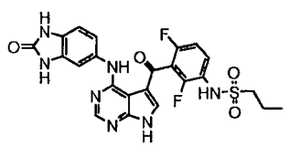
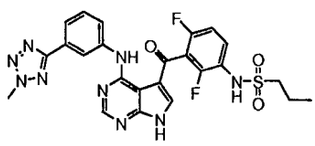
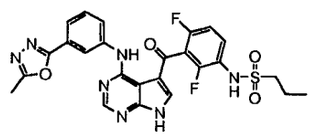
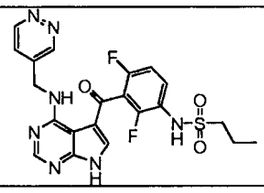
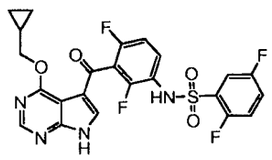
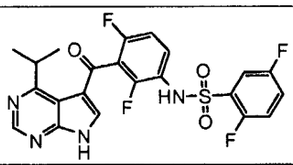
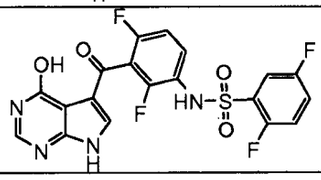
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P-1131		6-Methyl-pyridine-2-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	487.5
P-1132		Pyridine-3-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	473.0
P-1133		Pyridine-2-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	473.0
P-1134		Propane-1-sulfonic acid {3-[4-(benzo[1,2,5]thiadiazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	530.0
P-1135		N-[3-(4-Benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide	556.0
P-1136		N-{2,4-Difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide	543.5
P-1137		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide	520.5
P-1138		N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide	494.0
P-1139		N-{2,4-Difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide	572.0

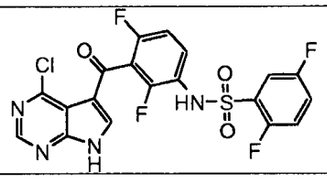
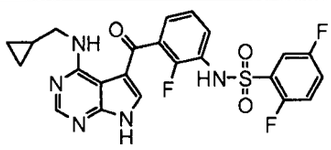
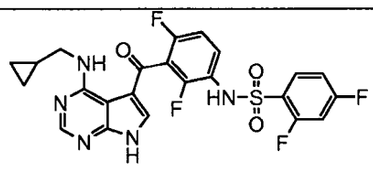
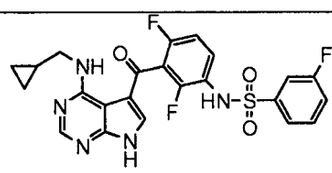
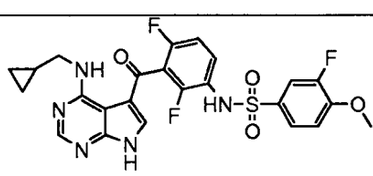
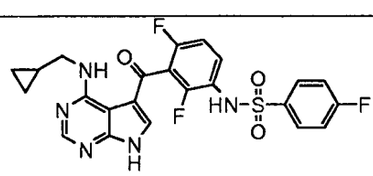
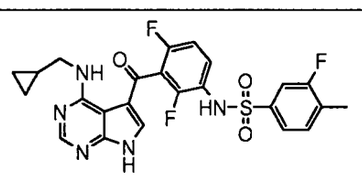
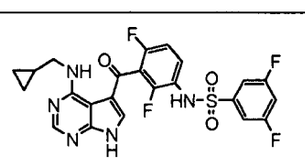
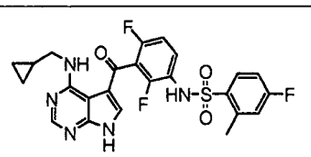
P-1140		N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide	522.0
P-1141		N-[2,4-Difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide	556.0
P-1142		N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide	560.0
P-1143		N-{3-[4-(1,3-Dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide	560.0
P-1144		N-[3-(4-Benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide	538.5
P-1145		N-{2,4-Difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide	525.5
P-1146		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide	502.0
P-1147		N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide	516.5
P-1148		N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide	476.0

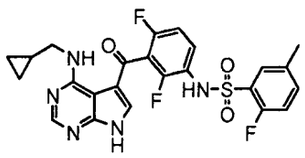
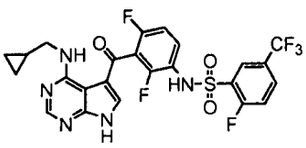
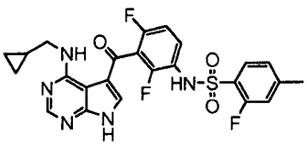
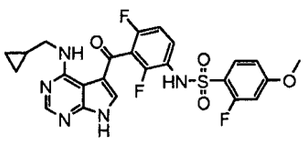
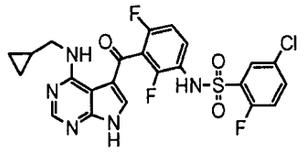
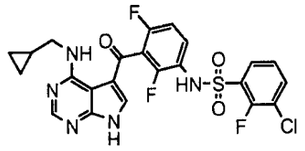
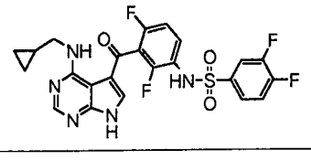
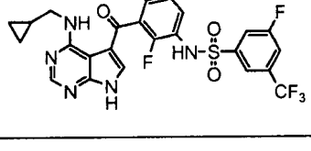
P-1149		N-{2,4-Difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide	554.0
P-1150		N-{2,4-Difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide	506.0
P-1151		N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide	504.0
P-1152		N-[2,4-Difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide	538.5
P-1153		N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide	542.0
P-1154		N-{3-[4-(1,3-Dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide	542.0
P-1155		N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-benzenesulfonamide	472.5
P-1156		Dimethylamine-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide	439.0
P-1157		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1H-indazol-6-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	512.0

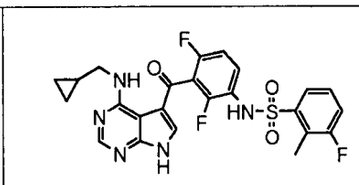
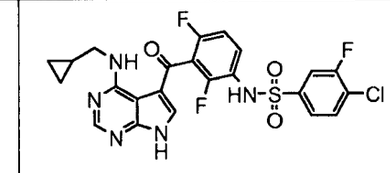
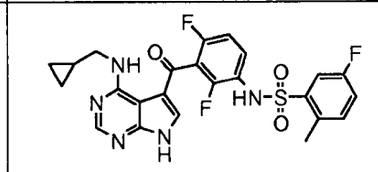
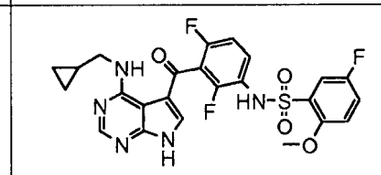
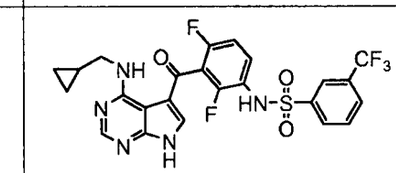
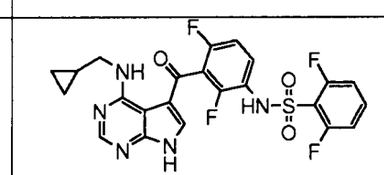
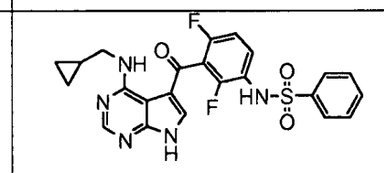
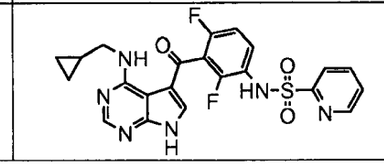
P-1158		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1H-indazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	512.0
P-1159		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(4-hydroxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	489.1
P-1160		Propane-1-sulfonic acid (2,4-difluoro-3-{4-[(5-methyl-1H-pyrazol-3-ylmethyl)-amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide	488.0 $[M-H^+]^-$
P-1161		3-({5-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino}-methyl)-benzoic acid	530.0
P-1162		4-{5-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino}-benzoic acid methyl ester	530.0
P-1163		4-{5-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino}-benzoic acid	516.0
P-1164		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-[1,2,4]triazol-1-yl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	539.5
P-1165		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-oxazol-5-yl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	539.5
P-1166		Propane-1-sulfonic acid (2,4-difluoro-3-{4-[(pyridin-3-ylmethyl)-amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide	487.5

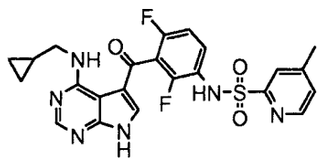
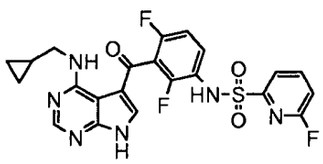
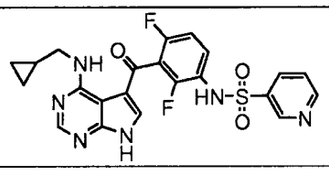
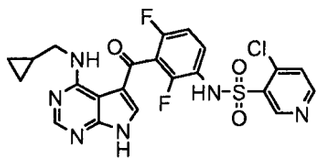
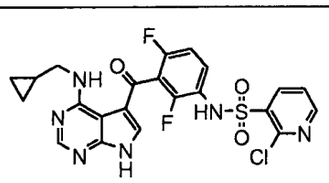
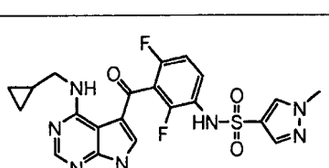
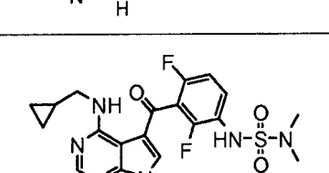
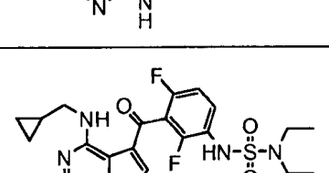
P-1167		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-[1,2,4]triazol-1-yl-propylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	505.0
P-1168		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-pyridin-3-yl-propylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	515.5
P-1169		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-hydroxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	488.0
P-1170		Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(5-methyl-4H-[1,2,4]triazol-3-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide	553.5
P-1171		Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(5-methyl-tetrazol-1-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide	554.0
P-1172		Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(4H-[1,2,4]triazol-3-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide	539.5
P-1173		Propane-1-sulfonic acid (3-{4-[(benzo[1,2,5]oxadiazol-5-ylmethyl)-amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-2,4-difluoro-phenyl)-amide	528.0
P-1174		Propane-1-sulfonic acid {3-[4-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	528.0
P-1175		Propane-1-sulfonic acid {3-[4-(1,1-dioxo-tetrahydro-1lambda*6*-thiophen-3-ylamino)-7H-pyrrolo[2,3-	514.5

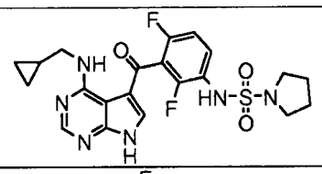
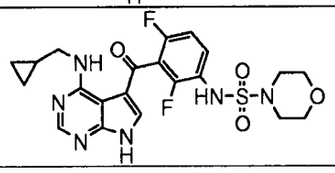
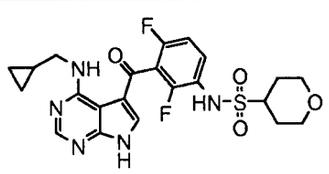
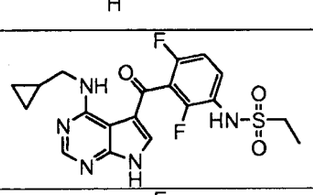
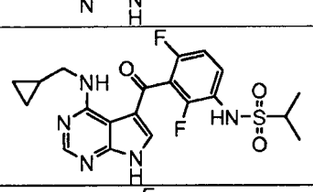
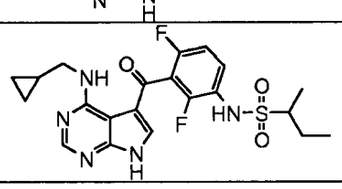
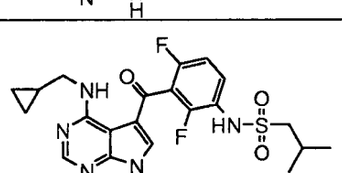
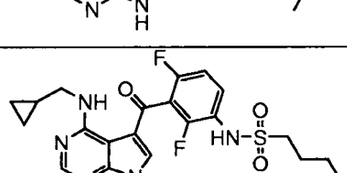
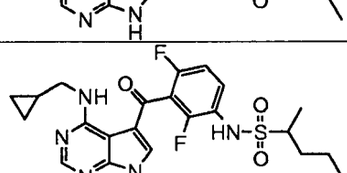
		d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	
P-1176		Propane-1-sulfonic acid (2,4-difluoro-3-{4-[2-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide	505.0
P-1177		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide	528.0
P-1178		Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(2-methyl-2H-tetrazol-5-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide	554.0
P-1179		Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide	554.0
P-1180		Propane-1-sulfonic acid (2,4-difluoro-3-{4-[(pyridazin-4-ylmethyl)-amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide	488.0
P-1181		N-[3-(4-Cyclopropylmethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide	521.0
P-1182		N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide	493.0
P-1183		N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide	466.9

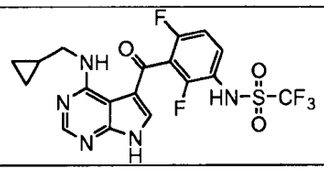
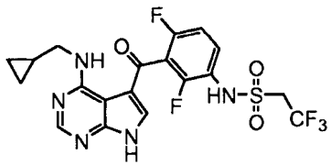
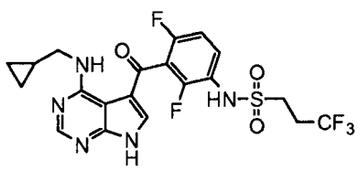
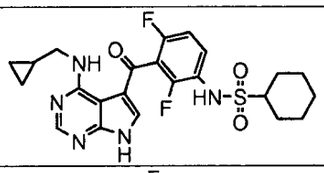
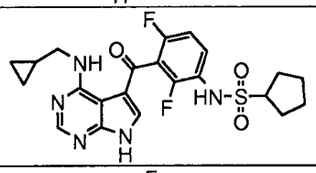
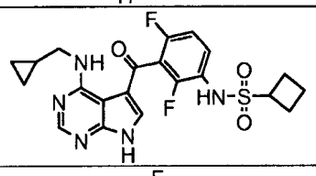
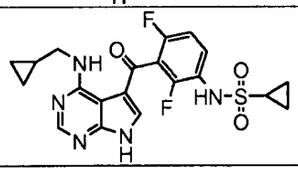
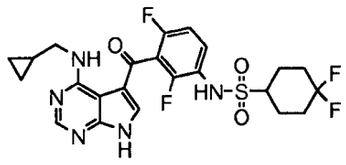
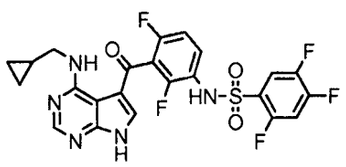
P-1184		N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide	
P-1185		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2-fluoro-phenyl}-2,5-difluoro-benzenesulfonamide	502.0
P-1186		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,4-difluoro-benzenesulfonamide	520.5
P-1187		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-benzenesulfonamide	502.0
P-1188		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-4-methoxy-benzenesulfonamide	
P-1189		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-fluoro-benzenesulfonamide	502.0
P-1190		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-4-methyl-benzenesulfonamide	516.5
P-1191		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3,5-difluoro-benzenesulfonamide	520.5
P-1192		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-fluoro-2-methyl-	516.5

		benzenesulfonamide	
P-1193		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-5-methyl-benzenesulfonamide	516.5
P-1194		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-5-trifluoromethyl-benzenesulfonamide	570.5
P-1195		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-4-methyl-benzenesulfonamide	516.5
P-1196		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-4-methoxy-benzenesulfonamide	532.0
P-1197		5-Chloro-N-{3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide	
P-1198		3-Chloro-N-{3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide	536.0
P-1199		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3,4-difluoro-benzenesulfonamide	520.5
P-1200		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-5-trifluoromethyl-benzenesulfonamide	570.5

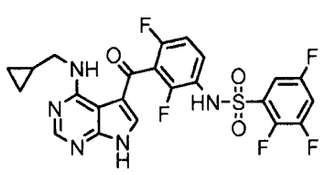
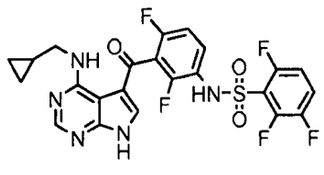
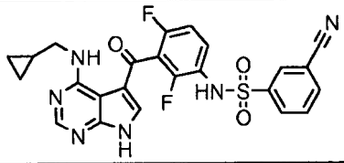
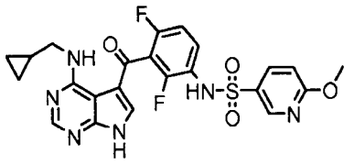
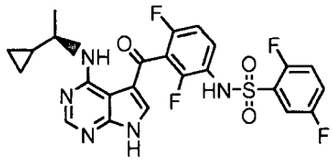
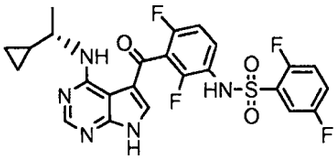
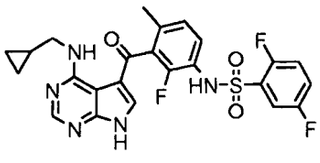
P-1201		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-2-methyl-benzenesulfonamide	516.5
P-1202		4-Chloro-N-{3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-benzenesulfonamide	536.0
P-1203		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-5-fluoro-2-methyl-benzenesulfonamide	516.5
P-1204		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-5-fluoro-2-methoxy-benzenesulfonamide	532.0
P-1205		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-trifluoromethyl-benzenesulfonamide	552.5
P-1206		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,6-difluoro-benzenesulfonamide	520.5
P-1207		N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-benzenesulfonamide	484.5
P-1208		Pyridine-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	485.5

P-1209		4-Methyl-pyridine-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	
P-1210		6-Fluoro-pyridine-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	
P-1211		Pyridine-3-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	
P-1212		4-Chloro-pyridine-3-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	
P-1213		2-Chloro-pyridine-3-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	519.0
P-1214		1-Methyl-1H-pyrazole-4-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	488.5
P-1215		N,N-Dimethylamino-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	451.0
P-1216		N,N-Diethylamino-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	479.0

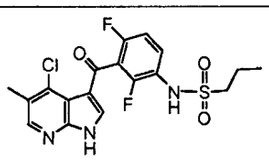
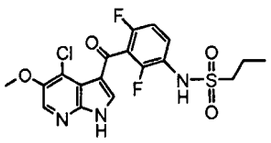
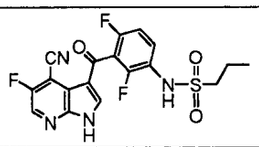
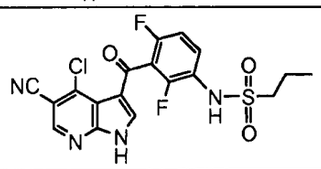
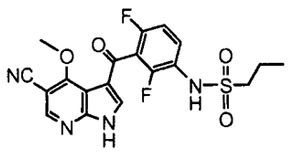
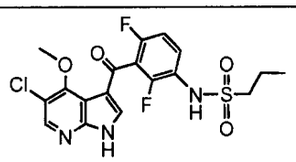
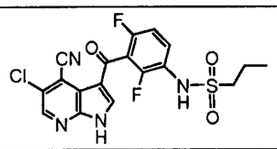
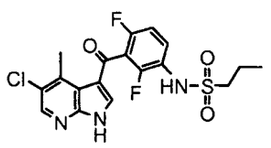
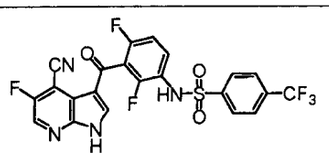
P-1217		Pyrrolidine-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	
P-1218		Morpholine-4-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	493.5
P-1219		Tetrahydro-pyran-4-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	
P-1220		Ethanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	
P-1221		Propane-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	450.0
P-1222		Butane-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	
P-1223		2-Methyl-propane-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	464.0
P-1224		Butane-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	464.0
P-1225		Pentane-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	478.0

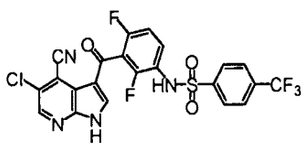
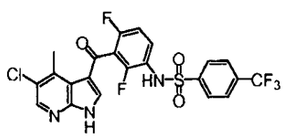
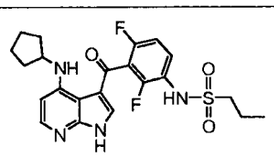
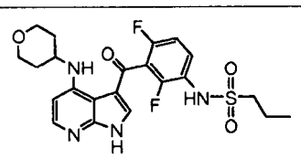
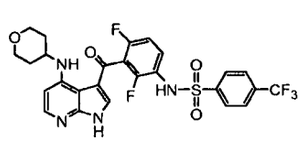
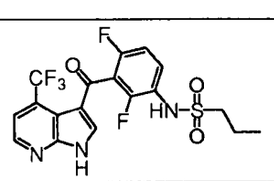
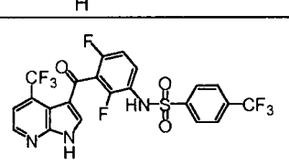
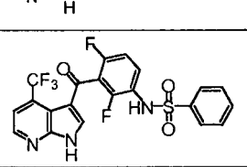
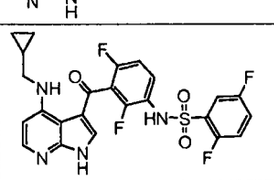
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P-1227		2,2,2-Trifluoro-ethanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	490.0
P-1228		3,3,3-Trifluoro-propane-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	504.0
P-1229		Cyclohexanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	490.5
P-1230		Cyclopentanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	476.0
P-1231		Cyclobutanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	462.5
P-1232		Cyclopropanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	448.0
P-1233		4,4-Difluoro-cyclohexanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide	
P-1234		N-[3-[4-(cyclopropylmethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl]-2,4,5-trifluoro-benzenesulfonamide	538.5

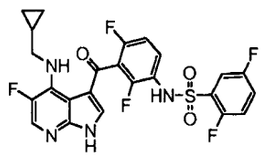
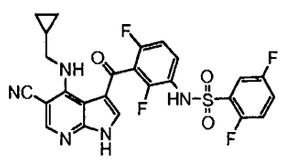
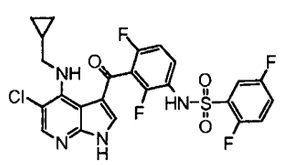
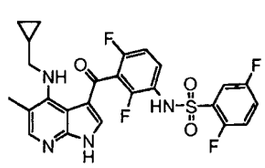
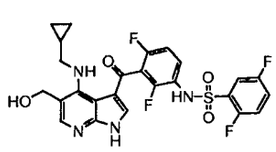
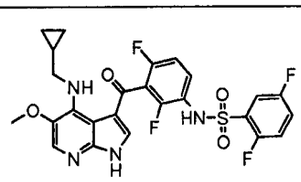
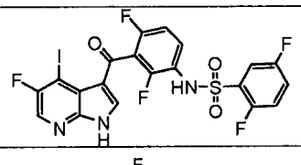
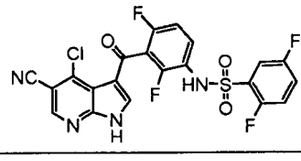
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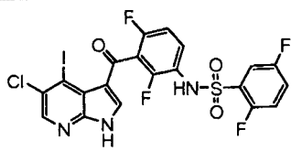
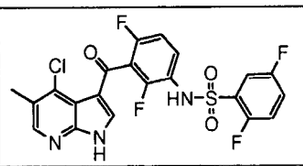
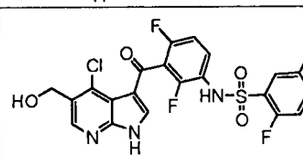
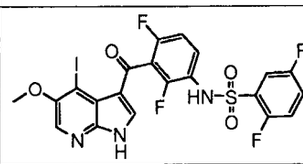
P-1235		N-[3-[4-(cyclopropylmethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl]-2,3,5-trifluoro-benzenesulfonamide	538.5
P-1236		N-[3-[4-(cyclopropylmethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl]-2,3,6-trifluoro-benzenesulfonamide	538.5
P-1237		3-cyano-N-[3-[4-(cyclopropylmethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl]benzenesulfonamide	509.0
P-1238		N-[3-[4-(cyclopropylmethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl]-6-methoxy-pyridine-3-sulfonamide	
P-1239		N-[3-[4-[[(1R)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide	534.5
P-1240		N-[3-[4-[[(1S)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide	534.5
P-1241		N-[3-[4-(cyclopropylmethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2-fluoro-4-methyl-phenyl]-2,5-difluoro-benzenesulfonamide	

[0054] In various aspects and embodiments, provided are the compounds shown in Table II below, and/or pharmaceutically acceptable salts of the compounds shown in Table II.

P-2001		Propane-1-sulfonic acid [3-(4-chloro-5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide	427.9/ 429.9
P-2002		Propane-1-sulfonic acid [3-(4-chloro-5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide	443.9/ 446.1
P-2003		Propane-1-sulfonic acid [3-(4-cyano-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide	421.4
P-2004		Propane-1-sulfonic acid [3-(4-chloro-5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide	439.1
P-2005		Propane-1-sulfonic acid [3-(5-cyano-4-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide	435.1
P-2006		Propane-1-sulfonic acid [3-(5-chloro-4-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide	444.1
P-2007		Propane-1-sulfonic acid [3-(5-chloro-4-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide	437.4/ 439.5
P-2008		Propane-1-sulfonic acid [3-(5-chloro-4-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide	428.1/ 430.1
P-2009		N-[3-(4-Cyano-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide	523.3

P-2010		N-[3-(5-Chloro-4-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide	539.3/ 541.3
P-2011		N-[3-(5-Chloro-4-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide	530.0/ 532.4
P-2012		Propane-1-sulfonic acid [3-(4-cyclopentylamino-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide	463.8
P-2013		Propane-1-sulfonic acid {2,4-difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide	479.1
P-2014		N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide	581.4
P-2015		Propane-1-sulfonic acid [2,4-difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	447.9
P-2016		N-[2,4-Difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide	549.9
P-2017		N-[2,4-Difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide	481.9
P-2018		N-{3-[4-(Cyclopropylmethyl-amino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide	519.1

P-2019		N-{3-[4-(Cyclopropylmethyl-amino)-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide	535.1
P-2020		N-{3-[5-Cyano-4-(cyclopropylmethyl-amino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide	544.0
P-2021		N-{3-[5-Chloro-4-(cyclopropylmethyl-amino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide	
P-2022		N-{3-[4-(Cyclopropylmethyl-amino)-5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide	
P-2023		N-{3-[4-(Cyclopropylmethyl-amino)-5-hydroxymethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide	
P-2024		N-{3-[4-(Cyclopropylmethyl-amino)-5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide	
P-2025		N-[2,4-Difluoro-3-(5-fluoro-4-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide	593.8
P-2026		N-[3-(4-Chloro-5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide	508.9/ 510.9

P-2027		N-[3-(5-Chloro-4-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide	
P-2028		N-[3-(4-Chloro-5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide	
P-2029		N-[3-(4-Chloro-5-hydroxymethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide	
P-2030		N-[2,4-Difluoro-3-(4-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide	

[0055] In one embodiment of compounds contemplated herein, the compound is selected from the group consisting of:

N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1011**),

N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1013**),

N-[2,4-Difluoro-3-(4-morpholin-4-yl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1017**),

N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1020**),

N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1024**),

N-[2,4-Difluoro-3-(4-methylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1026**),

N-[3-(4-Amino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1031**),

N-[2,4-Difluoro-3-(4-propylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-

benzenesulfonamide (**P-1032**),
N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1035**),
N-[2,4-Difluoro-3-(4-phenylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1037**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1039**),
N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1040**),
Propane-1-sulfonic acid [3-(4-cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1041**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide (**P-1042**),
N-{2,4-Difluoro-3-[4-(2-hydroxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1043**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1044**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3,5-dimethyl-benzenesulfonamide (**P-1045**),
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-1046**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1047**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-phenylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1048**),
N-[3-(4-Dimethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1049**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1050**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1051**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1052**),

N-{2,4-Difluoro-3-[4-(tetrahydro-furan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1054**),

N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1055**),

N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-1056**),

N-{2,4-Difluoro-3-[4-(1-methyl-piperidin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1057**),

N-{2,4-Difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1058**),

N-{3-[4-(2-Dimethylamino-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1059**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1060**),

N-[2,4-Difluoro-3-(4-pyrrolidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1061**),

N-{2,4-Difluoro-3-[4-(1-methyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1062**),

N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1063**),

N-[2,4-Difluoro-3-(4-hydroxyamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1064**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(4-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1065**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-hydrazino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1066**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(naphthalen-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1067**),

Propane-1-sulfonic acid (2,4-difluoro-3-{4-[(oxetan-3-ylmethyl)-amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1068**),

N-{2,4-Difluoro-3-[4-(4-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1069**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(naphthalen-1-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-

carbonyl]-phenyl}-amide (**P-1072**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1073**),
Propane-1-sulfonic acid [3-(4-benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1074**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-propylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1075**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(pyridin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1076**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1077**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1078**),
Propane-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1079**),
Propane-1-sulfonic acid {3-[4-(1-benzyl-pyrrolidin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1080**),
Propane-1-sulfonic acid [3-(4-cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1081**),
Propane-1-sulfonic acid [3-(4-ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1082**),
Propane-1-sulfonic acid {3-[4-(3-dimethylamino-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1083**),
Propane-1-sulfonic acid {3-[4-(3-chloro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1084**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1085**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1086**),
Propane-1-sulfonic acid {3-[4-(4-chloro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1087**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1088**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(4-trifluoromethyl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1089**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(6-methoxy-pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1090**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-trifluoromethyl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1091**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1092**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-p-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1093**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1094**),
Propane-1-sulfonic acid {3-[4-(1-ethyl-piperidin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1095**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1-methanesulfonyl-piperidin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1096**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(tetrahydro-furan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1097**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-methylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1098**),
Propane-1-sulfonic acid {3-[4-(1-ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1099**),
Propane-1-sulfonic acid {3-[4-(1,3-dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1100**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(2-fluoro-4-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1101**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1-methyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1102**),
N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1103**),
N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1104**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-fluoro-5-methoxy-pyridin-2-ylamino)-7H-pyrrolo[2,3-

d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1105**),
Propane-1-sulfonic acid [2-fluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1106**),
4-Cyano-N-[2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-benzenesulfonamide (**P-1108**),
2,2,2-Trifluoro-ethanesulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1109**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-difluoromethoxy-benzenesulfonamide (**P-1110**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1111**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,6-difluoro-benzenesulfonamide (**P-1112**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,4-difluoro-benzenesulfonamide (**P-1113**),
Propane-2-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1114**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-fluoro-benzenesulfonamide (**P-1115**),
3-Cyano-N-[2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-benzenesulfonamide (**P-1116**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-fluoro-4-methoxy-benzenesulfonamide (**P-1117**),
3,3,3-Trifluoro-propane-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1118**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-difluoromethoxy-benzenesulfonamide (**P-1119**),
1-Ethyl-1H-pyrazole-4-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1120**),
1-Methyl-1H-pyrazole-4-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1121**),
Piperidine-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1122**),

Cyclohexanesulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1123**),
Cyclopentanesulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1124**),
Pyrrolidine-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1125**),
2-Methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1126**),
Diethylamine-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1127**),
Cyclobutanesulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1128**),
Morpholine-4-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1129**),
6-Methoxy-pyridine-3-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1130**),
6-Methyl-pyridine-2-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1131**),
Pyridine-3-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1132**),
Pyridine-2-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1133**),
Propane-1-sulfonic acid {3-[4-(benzo[1,2,5]thiadiazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1134**),
N-[3-(4-Benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1135**),
N-{2,4-Difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1136**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1137**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1138**),
N-{2,4-Difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-

difluoro-benzenesulfonamide (**P-1139**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1140**),
N-[2,4-Difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1141**),
N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1142**),
N-{3-[4-(1,3-Dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1143**),
N-[3-(4-Benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1144**),
N-{2,4-Difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1145**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1146**),
N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1147**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1148**),
N-{2,4-Difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1149**),
N-{2,4-Difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1150**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1151**),
N-[2,4-Difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1152**),
N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1153**),
N-{3-[4-(1,3-Dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1154**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-benzenesulfonamide (**P-1155**),

Dimethylamine-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1156**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1H-indazol-6-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1157**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1H-indazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1158**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(4-hydroxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1159**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[(5-methyl-1H-pyrazol-3-ylmethyl)-amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1160**),
3-({5-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino}-methyl)-benzoic acid (**P-1161**),
4-{5-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino}-benzoic acid methyl ester (**P-1162**),
4-{5-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino}-benzoic acid (**P-1163**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-[1,2,4]triazol-1-yl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1164**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-oxazol-5-yl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1165**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[(pyridin-3-ylmethyl)-amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1166**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-[1,2,4]triazol-1-yl-propylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1167**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-pyridin-3-yl-propylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1168**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-hydroxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1169**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(5-methyl-4H-[1,2,4]triazol-3-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1170**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(5-methyl-tetrazol-1-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1171**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(4H-[1,2,4]triazol-3-yl)-phenylamino]-7H-pyrrolo[2,3-

d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1172**),
Propane-1-sulfonic acid (3-{4-[(benzo[1,2,5]oxadiazol-5-ylmethyl)-amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-2,4-difluoro-phenyl)-amide (**P-1173**),
Propane-1-sulfonic acid {3-[4-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1174**),
Propane-1-sulfonic acid {3-[4-(1,1-dioxo-tetrahydro-1lambda*6*-thiophen-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1175**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[2-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1176**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1177**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(2-methyl-2H-tetrazol-5-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1178**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1179**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[(pyridazin-4-ylmethyl)-amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1180**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2-fluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1185**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,4-difluoro-benzenesulfonamide (**P-1186**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-benzenesulfonamide (**P-1187**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-4-methoxy-benzenesulfonamide (**P-1188**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-fluoro-benzenesulfonamide (**P-1189**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-4-methyl-benzenesulfonamide (**P-1190**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3,5-difluoro-benzenesulfonamide (**P-1191**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-fluoro-2-methyl-benzenesulfonamide (**P-1192**),

N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-5-methyl-benzenesulfonamide (**P-1193**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-5-trifluoromethyl-benzenesulfonamide (**P-1194**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-4-methyl-benzenesulfonamide (**P-1195**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-4-methoxy-benzenesulfonamide (**P-1196**),
5-Chloro-N-{3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1197**),
3-Chloro-N-{3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1198**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3,4-difluoro-benzenesulfonamide (**P-1199**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-5-trifluoromethyl-benzenesulfonamide (**P-1200**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-2-methyl-benzenesulfonamide (**P-1201**),
4-Chloro-N-{3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-benzenesulfonamide (**P-1202**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-5-fluoro-2-methyl-benzenesulfonamide (**P-1203**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-5-fluoro-2-methoxy-benzenesulfonamide (**P-1204**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-trifluoromethyl-benzenesulfonamide (**P-1205**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,6-difluoro-benzenesulfonamide (**P-1206**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-benzenesulfonamide (**P-1207**),
Pyridine-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1208**),
4-Methyl-pyridine-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-

carbonyl]-2,4-difluoro-phenyl}-amide (**P-1209**),
6-Fluoro-pyridine-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1210**),
Pyridine-3-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1211**),
4-Chloro-pyridine-3-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1212**),
2-Chloro-pyridine-3-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1213**),
1-Methyl-1H-pyrazole-4-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1214**),
N,N-Dimethylamino-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1215**),
N,N-Diethylamino-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1216**),
Pyrrolidine-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1217**),
Morpholine-4-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1218**),
Tetrahydro-pyran-4-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1219**),
Ethanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1220**),
Propane-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1221**),
Butane-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1222**),
2-Methyl-propane-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1223**),
Butane-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1224**),
Pentane-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1225**),

N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-C,C,C-trifluoro-methanesulfonamide (**P-1226**),

2,2,2-Trifluoro-ethanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1227**),

3,3,3-Trifluoro-propane-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1228**),

Cyclohexanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1229**),

Cyclopentanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1230**),

Cyclobutanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1231**),

Cyclopropanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1232**),

4,4-Difluoro-cyclohexanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1233**),

3,3-Difluoro-cyclopentanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1234**),

3-Fluoro-cyclopentanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1235**),

Propane-1-sulfonic acid [3-(4-cyclopentylamino-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2012**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (**P-2013**),

N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-2014**),

N-{3-[4-(Cyclopropylmethyl-amino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-2018**),

N-{3-[4-(Cyclopropylmethyl-amino)-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-2019**),

N-{3-[5-Cyano-4-(cyclopropylmethyl-amino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-2020**),

N-{3-[5-Chloro-4-(cyclopropylmethyl-amino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-

phenyl}-2,5-difluoro-benzenesulfonamide (**P-2021**),
N-{3-[4-(Cyclopropylmethyl-amino)-5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-2022**),
N-{3-[4-(Cyclopropylmethyl-amino)-5-hydroxymethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-2023**),
N-{3-[4-(Cyclopropylmethyl-amino)-5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-2024**), and
any pharmaceutically acceptable salt thereof.

[0056] In one embodiment of compounds contemplated herein, the compound is selected from the group consisting of:
N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1011**),
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1013**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1020**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1024**),
N-[2,4-Difluoro-3-(4-methylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1026**),
N-[3-(4-Amino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1031**),
N-[2,4-Difluoro-3-(4-propylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1032**),
N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1035**),
N-[2,4-Difluoro-3-(4-phenylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1037**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1039**),
N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1040**),
Propane-1-sulfonic acid [3-(4-cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-

phenyl]-amide (**P-1041**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide (**P-1042**),
N-{2,4-Difluoro-3-[4-(2-hydroxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1043**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1044**),
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-1046**),
N-[3-(4-Dimethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1049**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1050**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1052**),
N-{2,4-Difluoro-3-[4-(tetrahydro-furan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1054**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1055**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-1056**),
N-{2,4-Difluoro-3-[4-(1-methyl-piperidin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1057**),
N-{2,4-Difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1058**),
N-{3-[4-(2-Dimethylamino-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1059**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1060**),
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-2014**), and
any pharmaceutically acceptable salt thereof.

[0057] In one embodiment of compounds contemplated herein, the compound is selected from the group consisting of:

N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1011**),

N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1013**),

N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1020**),

N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1024**),

N-[2,4-Difluoro-3-(4-methylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1026**),

N-[3-(4-Amino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1031**),

N-[2,4-Difluoro-3-(4-propylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1032**),

N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1035**),

N-[2,4-Difluoro-3-(4-phenylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1037**),

N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1039**),

N-{2,4-Difluoro-3-[4-(2-hydroxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1043**),

N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1044**),

N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-1046**),

N-[3-(4-Dimethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1049**),

N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1050**),

N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-

trifluoromethyl-benzenesulfonamide (**P-1052**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-1056**),
N-{2,4-Difluoro-3-[4-(1-methyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1062**),
N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1063**),
4-Cyano-N-[2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-benzenesulfonamide (**P-1108**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-difluoromethoxy-benzenesulfonamide (**P-1110**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-difluoromethoxy-benzenesulfonamide (**P-1119**),
1-Methyl-1H-pyrazole-4-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1121**), and
any pharmaceutically acceptable salt thereof.

[0058] In one embodiment of compounds contemplated herein, the compound is selected from the group consisting of:
Propane-1-sulfonic acid [3-(4-cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1041**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1060**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(4-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1065**),
N-{2,4-Difluoro-3-[4-(4-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1069**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(naphthalen-1-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1072**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1073**),
Propane-1-sulfonic acid [3-(4-benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1074**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-propylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-

phenyl]-amide (**P-1075**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1077**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1078**),
Propane-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1079**),
Propane-1-sulfonic acid [3-(4-cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1081**),
Propane-1-sulfonic acid [3-(4-ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1082**),
Propane-1-sulfonic acid {3-[4-(3-dimethylamino-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1083**),
Propane-1-sulfonic acid {3-[4-(3-chloro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1084**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1085**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1086**),
Propane-1-sulfonic acid {3-[4-(4-chloro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1087**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1088**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(4-trifluoromethyl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1089**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(6-methoxy-pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1090**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-trifluoromethyl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1091**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1092**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-p-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1093**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1094**),

Propane-1-sulfonic acid {3-[4-(1-ethyl-piperidin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1095**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1-methanesulfonyl-piperidin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1096**),

Propane-1-sulfonic acid {3-[4-(1-ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1099**),

Propane-1-sulfonic acid {3-[4-(1,3-dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1100**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(2-fluoro-4-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1101**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1-methyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1102**),

N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1103**),

N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1104**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-fluoro-5-methoxy-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1105**),

N-[3-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1107**),

N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1111**),

N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-fluoro-benzenesulfonamide (**P-1115**),

Piperidine-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1122**),

2-Methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1126**),

Pyridine-3-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1132**),

Propane-1-sulfonic acid {3-[4-(benzo[1,2,5]thiadiazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-

carbonyl]-2,4-difluoro-phenyl}-amide (**P-1134**),
N-[3-(4-Benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1135**),
N-{2,4-Difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1136**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1137**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1138**),
N-{2,4-Difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1139**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1140**),
N-[2,4-Difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1141**),
N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1142**),
N-{3-[4-(1,3-Dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1143**),
N-[3-(4-Benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1144**),
N-{2,4-Difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1145**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1146**),
N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1147**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1148**),
N-{2,4-Difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1149**),
N-{2,4-Difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1150**),

N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1151**),
N-[2,4-Difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1152**),
N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1153**),
N-{3-[4-(1,3-Dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1154**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1H-indazol-6-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1157**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1H-indazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1158**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(4-hydroxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1159**),
4-{5-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino}-benzoic acid methyl ester (**P-1162**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(5-methyl-tetrazol-1-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1171**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1177**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1179**), and
any pharmaceutically acceptable salt thereof.

[0059] In one embodiment of compounds contemplated herein, the compound is selected from the group consisting of:
N-{2,4-Difluoro-3-[4-(4-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1069**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1073**),
N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1103**),
N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1104**),

N-[3-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1107**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1111**),
N-[3-(4-Benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1135**),
N-{2,4-Difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1136**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1137**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1138**),
N-{2,4-Difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1139**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1140**),
N-[2,4-Difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1141**),
N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1142**),
N-{3-[4-(1,3-Dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1143**),
N-[3-(4-Benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1144**),
N-{2,4-Difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1145**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1146**),
N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1147**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1148**),
N-{2,4-Difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-

fluoro-benzenesulfonamide (**P-1149**),
N-{2,4-Difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1150**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1151**),
N-[2,4-Difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1152**),
N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1153**),
N-{3-[4-(1,3-Dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1154**), and
any pharmaceutically acceptable salt thereof.

[0060] In one embodiment of compounds contemplated herein, the compound is selected from the group consisting of:
N-{2,4-Difluoro-3-[4-(4-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1069**),
N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1104**),
N-[3-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1107**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1111**),
N-[3-(4-Benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1135**),
N-{2,4-Difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1136**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1137**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1138**),
N-{2,4-Difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1139**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-

benzenesulfonamide (**P-1140**),
N-[2,4-Difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1141**),
N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1142**),
N-{3-[4-(1,3-Dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1143**), and
any salt, prodrug, tautomer, or stereoisomer thereof.

[0061] In one embodiment of compounds contemplated herein, the compound is selected from the group consisting of:
Propane-1-sulfonic acid [3-(4-chloro-5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2001**),
Propane-1-sulfonic acid [3-(4-chloro-5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2002**),
Propane-1-sulfonic acid [3-(4-cyano-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2003**),
Propane-1-sulfonic acid [3-(4-chloro-5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2004**),
Propane-1-sulfonic acid [3-(5-cyano-4-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2005**),
Propane-1-sulfonic acid [3-(5-chloro-4-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2006**),
Propane-1-sulfonic acid [3-(5-chloro-4-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2007**),
Propane-1-sulfonic acid [3-(5-chloro-4-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2008**),
N-[3-(4-Cyano-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2009**),
N-[3-(5-Chloro-4-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2010**),
N-[3-(5-Chloro-4-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2011**),
N-[2,4-Difluoro-3-(5-fluoro-4-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-2,5-difluoro-

benzenesulfonamide (**P-2025**),
N-[3-(4-Chloro-5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-2026**),
N-[3-(5-Chloro-4-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-2027**),
N-[3-(4-Chloro-5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-2028**),
N-[3-(4-Chloro-5-hydroxymethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-2029**),
N-[2,4-Difluoro-3-(4-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-2030**), and
any pharmaceutically acceptable salt thereof.

[0062] In a fourth aspect, compounds are provided, wherein the compound is selected from the group consisting of:
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1001**),
Propane-1-sulfonic acid [3-(4-ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1002**),
2-Methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1003**),
2-Methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1004**),
N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1005**),
N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1006**),
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1007**),
N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide (**P-1008**),
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1009**),
N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-

benzenesulfonamide (**P-1010**),
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1012**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1014**),
N-[2,4-Difluoro-3-(4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1015**),
N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1016**),
6-Methoxy-pyridine-3-sulfonic acid [2,4-difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1018**),
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide (**P-1019**),
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1021**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1022**),
N-[3-(4-Cyano-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1023**),
N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3,5-dimethyl-benzenesulfonamide (**P-1025**),
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3,5-dimethyl-benzenesulfonamide (**P-1027**),
N-[2,4-Difluoro-3-(4-isobutoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1028**),
N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1029**),
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1030**),
Propane-1-sulfonic acid [3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1033**),
N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1034**),

N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-fluoro-4-methoxy-benzenesulfonamide (**P-1036**),
N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1038**),
N-[3-(4-Cyclopropylmethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1053**),
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1070**),
N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1071**),
N-[3-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1107**),
N-[3-(4-Cyclopropylmethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1181**),
N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1182**),
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1183**),
N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1184**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-2015**),
N-[2,4-Difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2016**),
N-[2,4-Difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide (**P-2017**), and
any pharmaceutically acceptable salt thereof.

[0063] In one embodiment of the fourth aspect the compound is selected from the group consisting of:
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1001**),
N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1005**),
N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-

benzenesulfonamide (**P-1006**),
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1007**),
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1012**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1014**),
N-[2,4-Difluoro-3-(4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1015**),
N-[2,4-Difluoro-3-(4-isobutoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1028**),
N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1029**),
N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1034**),
N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1038**),
N-[3-(4-Cyclopropylmethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1053**),
N-[2,4-Difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2016**), and
any pharmaceutically acceptable salt thereof.

[0064] In one embodiment of the fourth aspect the compound is selected from the group consisting of:
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1001**),
N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1005**),
N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1006**),
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1007**),
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1012**),

N-[2,4-Difluoro-3-(4-isobutoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1028**), and
any pharmaceutically acceptable salt thereof.

[0065] In one embodiment of the fourth aspect the compound is selected from the group consisting of:
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1009**),
N-[2,4-Difluoro-3-(4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1015**),
N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1016**),
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1021**),
N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1029**),
Propane-1-sulfonic acid [3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1033**),
N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1038**), and
any pharmaceutically acceptable salt thereof.

[0066] In one embodiment of the fourth aspect the compound is selected from the group consisting of:
Propane-1-sulfonic acid [2,4-difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1022**),
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1070**),
N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1071**),
N-[3-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1107**),
N-[3-(4-Cyclopropylmethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1181**),
N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-

benzenesulfonamide (**P-1182**), and
any pharmaceutically acceptable salt thereof.

[0067] In one embodiment of any of the above aspects and embodiments, the compound includes any prodrug thereof.

[0068] In one embodiment of any of the above aspects and embodiments, the compound includes any tautomer thereof.

[0069] In one embodiment of any of the above aspects and embodiments, the compound includes any stereoisomer thereof.

[0070] In one embodiment of any of the above aspects and embodiments, the compound includes any pharmaceutically acceptable formulation thereof.

[0071] In one embodiment of any of the above aspects and embodiments, the compound includes any conjugate thereof.

[0072] In one embodiment of any of the above aspects and embodiments, the compound includes any derivative thereof.

[0073] In one embodiment of any of the above aspects and embodiments, the compound includes any form thereof.

[0074] In reference to compounds described herein, unless clearly indicated to the contrary, specification of a compound or group of compounds includes salts of such compound(s) (including pharmaceutically acceptable salts), formulations of such compound(s) (including pharmaceutically acceptable formulations), conjugates thereof, derivatives thereof, forms thereof, prodrugs thereof, and all stereoisomers thereof. In reference to compositions, kits, methods of use, etc. of compounds as described herein, i.e. compounds of the invention, it is understood (unless indicated otherwise) that a compound as described herein includes compounds of Formula I including all sub-embodiments thereof, compounds of Formula II including all sub-embodiments thereof, and compounds as listed in the third aspect above, including all sub-embodiments thereof.

[0075] In a fifth aspect, methods are provided for treating any Raf 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.

[0076] In a sixth aspect, methods are provided 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.

[0077] In a seventh aspect, methods are provided for treating any B-Raf V600E 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.

[0078] In an eighth aspect, methods are provided for treating any c-Raf-1 protein kinase mediated disease or condition, including any c-Raf-1 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.

[0079] In a ninth aspect, 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 non-Raf kinases. In some embodiments, a compound as described herein will selectively inhibit one Raf kinase relative to one or more other Raf kinases. In some embodiments, the compound as described herein will selectively inhibit a mutation of the Raf kinase relative to the wild type kinase, for example B-Raf V600E mutant relative to wild type B-Raf.

[0080] In a tenth aspect, a compound as described herein is a B-Raf V600E 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 B-Raf V600E mutant kinase activity assay. In some embodiments, the compound is selective relative to other protein kinases, such that the ratio of IC_{50} for another kinase assessed comparably, divided by the IC_{50} for B-Raf V600E mutant kinase is >10, also >20, also >30, also >40, also >50, also >60, also >70, also >80, also >90, also >100, wherein the other protein kinase includes, but is not limited to CSK, Insulin receptor kinase, AMPK, PDGFR or VEGFR. In some embodiments, the compound is also selective relative to one or more other Raf kinases such that the ratio of IC_{50} for another Raf kinase assessed comparably, divided by the IC_{50} for B-Raf V600E mutant kinase is >10, also >20, also >30, also >40, also >50, also >60, also >70, also >80, also >90, also >100.

[0081] In an eleventh aspect, a compound as described herein is a c-Raf-1 inhbitor 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 c-Raf-1 kinase activity assay. In some embodiments, the compound is selective relative to other protein kinases, such that the ratio of IC_{50} for another kinase assessed comparably, divided by the IC_{50} for c-Raf-1 kinase is >10, also >20, also >30, also >40, also >50, also >60, also >70, also >80, also >90, also >100, wherein the other protein kinase includes, but is not limited to CSK, Insulin receptor kinase, AMPK, PDGFR or VEGFR. In some embodiments, the compound is also selective relative to one or more other Raf kinases such that the ratio of IC_{50} for another Raf kinase assessed comparably, divided by the IC_{50} for c-Raf-1 kinase is >10, also >20, also >30, also >40, also >50, also >60, also >70, also >80, also >90, also >100. In some embodiments, a c-Raf-1 inhibitor is selective relative relative to at least B-Raf and B-Raf V600E. In one embodiment, the c-Raf-1 inhibitor is a compound selected from the group consisting of:
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1009**),
N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1011**),
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1013**),
N-[2,4-Difluoro-3-(4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1015**),
N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1016**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-

benzenesulfonamide (**P-1020**),
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1021**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1024**),
N-[2,4-Difluoro-3-(4-methylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1026**),
N-[2,4-Difluoro-3-(4-isobutoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1028**),
N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1029**),
N-[3-(4-Amino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1031**),
N-[2,4-Difluoro-3-(4-propylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1032**),
N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1035**),
N-[2,4-Difluoro-3-(4-phenylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1037**),
N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1038**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1039**),
N-{2,4-Difluoro-3-[4-(2-hydroxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1043**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1044**),
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-1046**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1047**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-phenylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1048**),

N-[3-(4-Dimethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1049**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1050**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1052**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-1056**),
N-{2,4-Difluoro-3-[4-(1-methyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1062**),
N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1063**),
4-Cyano-N-[2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-benzenesulfonamide (**P-1108**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-difluoromethoxy-benzenesulfonamide (**P-1110**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-difluoromethoxy-benzenesulfonamide (**P-1119**),
1-Methyl-1H-pyrazole-4-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1121**),
N-[3-(4-Cyano-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2009**),
N-[3-(5-Chloro-4-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2010**),
N-[2,4-Difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide (**P-2017**), and
any pharmaceutically acceptable salt thereof.

[0082] In one embodiment, the c-Raf-1 inhibitor is a compound selected from the group consisting of:
N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1011**),
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1013**),
N-[2,4-Difluoro-3-(4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-

benzenesulfonamide (**P-1015**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1020**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1024**),
N-[2,4-Difluoro-3-(4-methylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1026**),
N-[2,4-Difluoro-3-(4-isobutoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1028**),
N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1029**),
N-[3-(4-Amino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1031**),
N-[2,4-Difluoro-3-(4-propylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1032**),
N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1035**),
N-[2,4-Difluoro-3-(4-phenylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1037**),
N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1038**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1039**),
N-{2,4-Difluoro-3-[4-(2-hydroxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1043**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1044**),
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-1046**),
N-[3-(4-Dimethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1049**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1050**),

N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1052**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-1056**),
N-[3-(5-Chloro-4-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2010**), and
any pharmaceutically acceptable salt thereof.

[0083] In one embodiment, the c-Raf-1 inhibitor is a compound selected from the group consisting of:
N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1011**),
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1013**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1020**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1024**),
N-[2,4-Difluoro-3-(4-methylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1026**),
N-[2,4-Difluoro-3-(4-isobutoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1028**),
N-[3-(4-Amino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1031**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1039**), and
any pharmaceutically acceptable salt thereof.

[0084] In a twelfth aspect, a compound as described herein is a pan Raf inhibitor, i.e. inhibits each of B-Raf V600E mutant kinase, B-Raf kinase and c-Raf-1 kinase, with an IC_{50} of 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 each of a generally accepted B-Raf V600E mutant kinase activity assay, B-Raf kinase activity assay, and c-Raf-1 kinase activity assay. In some embodiments, the compounds are effectively equipotent on each of B-Raf V600E, B-Raf and c-Raf-1, i.e. the ratio of IC_{50} for any of B-Raf V600E, B-Raf and c-Raf-1 divided by the IC_{50} for any other of B-Raf V600E, B-Raf and c-Raf-1 (e.g. B-Raf IC_{50} divided by B-Raf V600E IC_{50})

is in the range of 10 to 0.1, also 5 to 0.2. In some embodiments, the compound is selective relative to other protein kinases, such that the ratio of IC_{50} for another kinase assessed comparably, divided by the IC_{50} for any of B-Raf V600E, B-Raf and c-Raf-1 is >10, also >20, also >30, also >40, also >50, also >60, also >70, also >80, also >90, also >100, wherein the other protein kinase includes, but is not limited to CSK, Insulin receptor kinase, AMPK, PDGFR or VEGFR. In one embodiment, the pan Raf inhibitor is a compound selected from the group consisting of:

Propane-1-sulfonic acid [2,4-difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1022**),

N-[2,4-Difluoro-3-(4-propylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1032**),

N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1035**),

N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1039**),

Propane-1-sulfonic acid [3-(4-cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1041**),

N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide (**P-1042**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1047**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-phenylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1048**),

N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1050**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1051**),

N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1052**),

N-{2,4-Difluoro-3-[4-(tetrahydro-furan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1054**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1060**),

N-{2,4-Difluoro-3-[4-(1-methyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-

phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1062**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(4-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1065**),

N-{2,4-Difluoro-3-[4-(4-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1069**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(naphthalen-1-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1072**),

N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1073**),

Propane-1-sulfonic acid [3-(4-benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1074**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-propylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1075**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1077**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1078**),

Propane-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1079**),

Propane-1-sulfonic acid [3-(4-cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1081**),

Propane-1-sulfonic acid [3-(4-ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1082**),

Propane-1-sulfonic acid {3-[4-(3-dimethylamino-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1083**),

Propane-1-sulfonic acid {3-[4-(3-chloro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1084**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1085**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1086**),

Propane-1-sulfonic acid {3-[4-(4-chloro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1087**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1088**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(4-trifluoromethyl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1089**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(6-methoxy-pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1090**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-trifluoromethyl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1091**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1092**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-p-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1093**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1094**),

Propane-1-sulfonic acid {3-[4-(1-ethyl-piperidin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1095**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1-methanesulfonyl-piperidin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1096**),

Propane-1-sulfonic acid {3-[4-(1-ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1099**),

Propane-1-sulfonic acid {3-[4-(1,3-dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1100**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(2-fluoro-4-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1101**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1-methyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1102**),

N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1103**),

N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1104**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-fluoro-5-methoxy-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1105**),

N-[3-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-

benzenesulfonamide (**P-1107**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1111**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-fluoro-benzenesulfonamide (**P-1115**),
Piperidine-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1122**),
2-Methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1126**),
Pyridine-3-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1132**),
Propane-1-sulfonic acid {3-[4-(benzo[1,2,5]thiadiazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1134**),
N-[3-(4-Benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1135**),
N-{2,4-Difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1136**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1137**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1138**),
N-{2,4-Difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1139**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1140**),
N-[2,4-Difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1141**),
N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1142**),
N-{3-[4-(1,3-Dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1143**),
N-[3-(4-Benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1144**),

N-{2,4-Difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1145**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1146**),
N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1147**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1148**),
N-{2,4-Difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1149**),
N-{2,4-Difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1150**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1151**),
N-[2,4-Difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1152**),
N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1153**),
N-{3-[4-(1,3-Dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1154**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1H-indazol-6-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1157**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1H-indazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1158**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(4-hydroxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1159**),
4-{5-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino}-benzoic acid methyl ester (**P-1162**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(5-methyl-tetrazol-1-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1171**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1177**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenylamino]-7H-

pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1179**),
N-[3-(4-Cyclopropylmethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1181**),
N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1182**),
Propane-1-sulfonic acid [3-(4-chloro-5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2001**),
Propane-1-sulfonic acid [3-(4-chloro-5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2002**),
Propane-1-sulfonic acid [3-(4-cyano-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2003**),
Propane-1-sulfonic acid [3-(4-chloro-5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2004**),
Propane-1-sulfonic acid [3-(5-cyano-4-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2005**),
Propane-1-sulfonic acid [3-(5-chloro-4-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2006**),
Propane-1-sulfonic acid [3-(5-chloro-4-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2007**),
Propane-1-sulfonic acid [3-(5-chloro-4-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2008**),
N-[3-(4-Cyano-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2009**),
N-[3-(5-Chloro-4-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2010**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (**P-2013**), and
any pharmaceutically acceptable salt thereof.

[0085] In one embodiment, the pan Raf inhibitor is a compound selected from the group consisting of:
Propane-1-sulfonic acid [3-(4-cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1041**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide (**P-1042**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1051**),
N-{2,4-Difluoro-3-[4-(tetrahydro-furan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1054**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1060**),
Propane-1-sulfonic acid [3-(4-chloro-5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2001**),
Propane-1-sulfonic acid [3-(4-chloro-5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2002**),
Propane-1-sulfonic acid [3-(4-cyano-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2003**),
Propane-1-sulfonic acid [3-(4-chloro-5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2004**),
Propane-1-sulfonic acid [3-(5-cyano-4-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2005**),
Propane-1-sulfonic acid [3-(5-chloro-4-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2006**),
Propane-1-sulfonic acid [3-(5-chloro-4-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2007**),
Propane-1-sulfonic acid [3-(5-chloro-4-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2008**), and
any pharmaceutically acceptable salt thereof.

[0086] In one embodiment, the pan Raf inhibitor is a compound selected from the group consisting of:
N-[2,4-Difluoro-3-(4-propylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1032**),
N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1035**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1039**),
Propane-1-sulfonic acid [3-(4-cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1041**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-

benzenesulfonamide (**P-1042**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1050**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1052**),
N-{2,4-Difluoro-3-[4-(tetrahydro-furan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1054**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1060**),
N-[3-(5-Chloro-4-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2010**), and
any pharmaceutically acceptable salt thereof.

[0087] In one embodiment, the pan Raf inhibitor is a compound selected from the group consisting of:
Propane-1-sulfonic acid [3-(4-cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1041**),
Propane-1-sulfonic acid [3-(4-chloro-5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2001**),
Propane-1-sulfonic acid [3-(4-chloro-5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2002**),
Propane-1-sulfonic acid [3-(4-cyano-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2003**),
Propane-1-sulfonic acid [3-(5-cyano-4-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2005**),
Propane-1-sulfonic acid [3-(5-chloro-4-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2007**),
Propane-1-sulfonic acid [3-(5-chloro-4-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2008**), and
any pharmaceutically acceptable salt thereof.

[0088] In one embodiment, the pan Raf inhibitor is a compound selected from the group consisting of:
N-{2,4-Difluoro-3-[4-(4-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1069**),
N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-

benzenesulfonamide (**P-1104**),
N-[3-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1107**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1111**),
N-[3-(4-Benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1135**),
N-{2,4-Difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1136**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1137**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1138**),
N-{2,4-Difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1139**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1140**),
N-[2,4-Difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1141**),
N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1142**),
N-{3-[4-(1,3-Dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1143**),
N-[3-(4-Cyclopropylmethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1181**),
N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1182**), and
any pharmaceutically acceptable salt thereof.

[0089] In one embodiment, the pan Raf inhibitor is a compound selected from the group consisting of:
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1070**),
N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1071**),

N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1073**),
N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1103**),
N-[3-(4-Benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1144**),
N-{2,4-Difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1145**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1146**),
N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1147**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1148**),
N-{2,4-Difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1149**),
N-{2,4-Difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1150**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1151**),
N-[2,4-Difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1152**),
N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1153**),
N-{3-[4-(1,3-Dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1154**), and
any pharmaceutically acceptable salt thereof.

[0090] In a thirteenth aspect, compositions are provided that include a therapeutically effective amount of any one or more compound(s) as described herein and at least one pharmaceutically acceptable carrier, excipient, and/or diluent, including combinations of any two or more compounds as described herein. The composition can further include a plurality of different pharmacologically active compounds, which can include a plurality of compounds as described herein. In certain embodiments, the composition can include any one or more compound(s) as described herein along with one or more compounds that are

therapeutically effective for the same disease indication. 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.

[0091] In a fourteenth aspect, the invention provides methods for treating a disease or condition mediated by one or more Raf kinases (including A-Raf, B-Raf, and c-Raf-1 kinases), including mutations thereof, 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 one embodiment, the invention provides methods for treating a disease or condition mediated by one or more Raf kinases, 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.

[0092] In a fifteenth aspect, the invention provides methods for treating a disease or condition mediated by A-Raf kinase, including any mutations thereof, 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 one embodiment, the invention provides methods for treating a disease or condition mediated by A-Raf kinase, including any 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.

[0093] In a sixteenth aspect, the invention provides methods for treating a disease or condition mediated by B-Raf kinase, including any mutations thereof, 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 one embodiment, the invention provides methods for treating a disease or condition mediated by B-Raf kinase, including any 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.

[0094] In a seventeenth aspect, the invention provides methods for treating a disease or condition mediated by B-Raf V600E mutant kinase, 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 one embodiment, the invention provides methods for treating a disease or condition mediated by B-Raf V600E 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 V600E 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 V600E 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.

[0095] In an eighteenth aspect, the invention provides methods for treating a disease or condition mediated by c-Raf-1 kinase, including any mutations thereof, 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 one embodiment, the invention provides methods for treating a disease or condition mediated by c-Raf-1 kinase, including any 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.

[0096] In a nineteenth aspect, 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 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.

[0097] In a twentieth aspect, the invention provides a pharmaceutical composition including a compound and another drug/agent, wherein the compound used in the combination includes those as described herein, for example, as defined in the claims and described in Formula I, Formula II, Formula III, Formula IIIa, Table I, or Table II. The invention further provides a method for treating a Raf protein kinase mediated disease or condition in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound and another drug or a pharmaceutically acceptable salt thereof, wherein the compound used in the combination includes those as described herein, for example, as defined in the claims and described in Formula I, Formula II, Formula III, Formula IIIa, Table I, or Table II. In some embodiments, the invention provides a composition for, or 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 suitable chemotherapeutic agents. In one embodiment, the one or more suitable chemotherapeutic agents is 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). 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.

[0098] In a twenty-first aspect, the invention provides a method of treating a disease or condition in a subject in need thereof, by administering to the subject a therapeutically effective amount of any one or more compound(s) as described herein, a prodrug of such compound, a pharmaceutically acceptable salt of such compound or prodrug, or a pharmaceutically acceptable formulation of such compound or prodrug. The compound can be alone or can be part of a composition. In one embodiment, the invention provides a method of treating a disease or condition in a subject, by administering to the subject a therapeutically effective amount of any one or more compound(s) as described herein, a prodrug of such compound, a pharmaceutically acceptable salt of such compound or prodrug, or a pharmaceutically

acceptable formulation of such compound or prodrug in combination with one or more other suitable therapies for the disease or condition.

[0099] In a twenty-second aspect, the invention provides kits that include a compound 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 includes 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 is packaged in unit dose or single dose form, e.g., single dose pills, capsules, or the like.

[0100] In aspects and embodiments involving treatment of a disease or condition with any one or more compound(s) as described herein, the invention provides methods for treating an A-Raf-mediated, B-Raf-mediated and/or c-Raf-1-mediated disease or condition in a subject in need thereof (e.g. a 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), e.g., a disease or condition characterized by abnormal A-Raf, B-Raf, and/or c-Raf-1 activity (e.g. kinase activity). In some embodiments, invention methods may involve administering to the subject suffering from or at risk of an A-Raf-mediated, B-Raf-mediated and/or c-Raf-1-mediated disease or condition an effective amount of any one or more Raf inhibitor(s) as described herein. In one embodiment, the A-Raf-mediated, B-Raf-mediated, and/or c-Raf-1-mediated disease is 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, 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.

[0101] In aspects and embodiments involving treatment of a disease or condition with any one or more compound(s) as described herein, the invention provides methods for treating a c-Raf-1-mediated disease or condition in a subject in need thereof (e.g. a 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), e.g., a disease or condition characterized by abnormal c-Raf-1 activity (e.g. kinase activity). In some embodiments, invention methods may involve administering to the subject suffering from or at risk of a c-Raf-1-mediated disease or condition an effective amount of any one or more c-Raf-1 inhibitor(s) as described herein. In one embodiment, the c-Raf-1-mediated disease is selected from the group consisting of polycystic kidney disease, acute pain, and chronic pain.

[0102] In aspects and embodiments involving treatment of a disease or condition with any one or more compound(s) as described herein, the invention provides methods for treating a B-Raf V600E mutant-mediated disease or condition in a subject in need thereof (e.g. a 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), e.g., a disease or condition characterized by abnormal B-Raf V600E mutant activity (e.g. kinase activity). In some embodiments, invention methods may involve administering to the subject suffering from or at risk of a B-Raf V600E mutant-mediated disease or condition an effective amount of any one or more B-Raf V600E inhibitor(s) as described herein. In one embodiment, B-Raf V600E mutant-mediated disease is a cancer, preferably a cancer 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.

[0103] In aspects and embodiments involving treatment of a disease or condition with any one or more compound(s) as described herein, the invention provides methods for treating a cancer in a subject in need thereof (e.g. a 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). In some embodiments, invention methods may involve administering to the subject suffering from or at risk of a cancer an effective amount of any one or more pan Raf inhibitor(s) as described herein, wherein the cancer is 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.

[0104] In a twenty-third aspect, any one or more compound(s) as described herein can be used in the preparation of a medicament for the treatment of an A-Raf-mediated, B-Raf-mediated or c-Raf-1-mediated disease or condition 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, 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, 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.

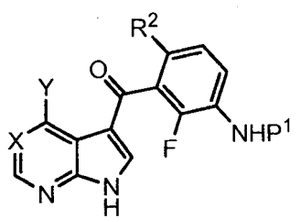
[0105] In a twenty-fourth aspect, any one or more c-Raf-1 inhibitor(s) as described herein can be used in the preparation of a medicament for the treatment of a c-Raf-1-mediated disease or condition selected from the group consisting of acute pain, chronic pain, and polycystic kidney disease.

[0106] In a twenty-fifth aspect, any one or more B-Raf V600E inhibitor(s) as described herein can be used in the preparation of a medicament for the treatment of a B-Raf-V600E-mediated disease or condition 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.

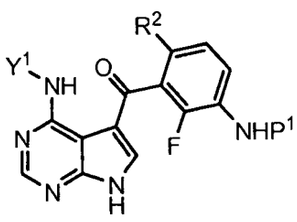
[0107] In a twenty-sixth aspect, any one or more pan Raf inhibitor(s) as described herein can be used in the preparation of a medicament for the treatment of a cancer selected from the group consisting of melanoma, glioma, glioblastoma, pilocytic astrocytoma, liver cancer, biliary tract cancer, cholangiocarcinoma, 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.

[0108] In various aspects and embodiments, a compound as disclosed herein (including any compounds of Formula I, Formula II, Formula III, Formula IIIa, Table I, Table II, or any other compounds specifically disclosed herein) is a pan Raf inhibitor. In various aspects and embodiments, a compound as disclosed herein (including any compounds of Formula I, Formula II, Formula III, Formula IIIa, Table I, Table II, or any other compounds specifically disclosed herein) is a Ras activity inhibitor. In some embodiments, a compound as disclosed herein (including any compounds of Formula I, Formula II, Formula III, Formula IIIa, Table I, Table II, or any other compounds specifically disclosed herein) is both a pan Raf inhibitor and a Ras activity inhibitor. In certain embodiments, a compound as disclosed herein (including any compounds of Formula I, Formula II, Formula III, Formula IIIa, Table I, Table II or any other compounds specifically disclosed herein) is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases and is a Ras activity inhibitor that inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 1 μM.

[0109] In another aspect, the invention provides an intermediate compound of Formulas IVa and IVb:



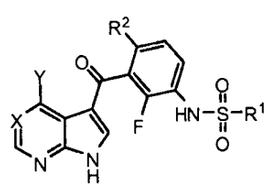
IVa



IVb

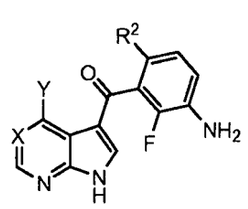
wherein P^1 is independenly H or an amino protecting group. In one embodiment, P^1 is H. In another embodiment, P^1 is t-butoxycarbonyl or benzyloxycarbonyl. In another embodiment, X is –N=, –CH=, -$C(CH_3)$=, -$C(OCH_3)$=, -C(F)=, -C(CN)=, -$C(CH_2OH)$= or –C(Cl)=. In certain instances, X is –CH=. In other instances, X is –N=. The other substituents X, Y, Y^1 and R^2 are as defined in any of the embodiments for compounds of Formulas I, II, III and IIIa described herein.

[0110] In another aspect, the invention provides a method for preparing a compound of Formula I



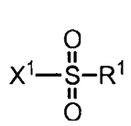
I

The method includes contacting a compound of Formula IVc:



IVc

with a compound of Formula V:

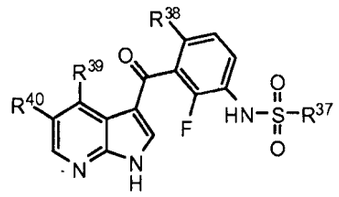


V

under conditions sufficient to form the compound of Formula I, wherein X^1 is a halogen, such as Cl, Br or I, the other variables R^1, R^2, X and Y are as defined in any of the embodiments for compounds of

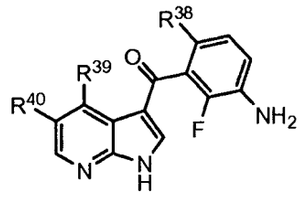
Formulas I, II, III and IIIa described herein and in the Examples below. In some embodiments, X is –N=, –CH=, -C(CH_3)=, -C(OCH_3)=, -C(F)=, -C(CN)=, -C(CH_2OH)= or –C(Cl)=. In a preferred embodiment, R^1 is 2-fluorophenyl, 3-fluorophenyl, 2,5-difluorophenyl or 4-lower alkyl-substituted phenyl, wherein lower alkyl is optionally substituted with one or more fluorine.

[0111] In some embodiments, the invention provides a method for preparing a compound of Formula II:



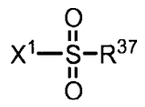
II

The method includes contacting a compound of Formula IVd:



IVd

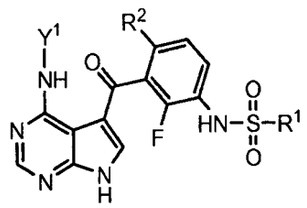
with a compound of Formula Va:



Va

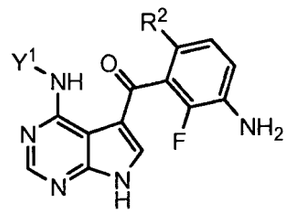
under conditions suitable to form the compound of Formula I, wherein X^1 is a halogen, such as Cl, Br or I, the other variables R^{37}, R^{38}, R^{39} and R^{40} are as defined in any of the embodiments for compounds of Formulas II described herein and in the Examples below. In a preferred embodiment, R^{37} is 2-fluorophenyl, 3-fluorophenyl, 2,5-difluorophenyl or 4-lower alkyl-substituted phenyl, wherein lower alkyl is optionally substituted with one or more fluorine.

[0112] In some embodiments, the invention provides a method for preparing a compound of Formula IIIa:



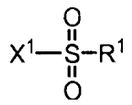
IIIa

The method includes contacting a compound of Formula IVe:



IVe

with a compound of Formula V:



V

under conditions sufficient to form the compound of Formula I, wherein X^1 is a halogen, such as Cl, Br or I, the other variables Y^1, R^1 and R^2 are as defined in any of the embodiments above for compounds of Formulas I and IIIa and in the Examples below. In a preferred embodiment, R^1 is 2-fluorophenyl, 3-fluorophenyl, 2,5-difluorophenyl or 4-lower alkyl-substituted phenyl, wherein lower alkyl is optionally substituted with one or more fluorine.

[0113] Additional aspects and embodiments will be apparent from the following Detailed Description of the Invention and from the claims.

DETAILED DESCRIPTION OF THE INVENTION

[0114] As used herein the following definitions apply unless clearly indicated otherwise:

[0115] All atoms designated within a Formula described herein, either within a structure provided, or within the definitions of variables related to the structure, is intended to include any isotope thereof, unless clearly indicated to the contrary. It is understood that for any given atom, the isotopes may be present essentially in ratios according to their natural occurrence, or one or more particular atoms may be enhanced with respect to one or more isotopes using synthetic methods known to one skilled in the art.

Thus, hydrogen includes for example ^{1}H, ^{2}H, ^{3}H; carbon includes for example ^{11}C, ^{12}C, ^{13}C, ^{14}C; oxygen includes for example ^{16}O, ^{17}O, ^{18}O; nitrogen includes for example ^{13}N, ^{14}N, ^{15}N; sulfur includes for example ^{32}S, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{37}S, ^{38}S; fluoro includes for example ^{17}F, ^{18}F, ^{19}F; chloro includes for example ^{35}Cl, ^{36}Cl, ^{37}Cl, ^{38}Cl, ^{39}Cl; and the like.

[0116] "Halogen" refer to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

[0117] "Haloalkyl or Halogen substituted lower alkyl" includes alkyl substituted by one to seven halogen atoms. Haloalkyl includes monohaloalkyl and polyhaloalkyl. For example, the term "haloalkyl" is meant to include trifluoromethyl, CF_3CH_2-, CF_2HCH_2-, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0118] "Haloalkoxy" refers to a -OR radical where R is haloalkyl group as defined above, e. g., trifluoromethoxy, 2,2, 2-trifluoroethoxy, difluoromethoxy, and the like.

[0119] "Hydroxyl" or "hydroxy" refer to the group -OH.

[0120] "Thiol" refers to the group -SH.

[0121] "Lower alkyl" alone or in combination means an alkane-derived radical containing from 1 to 6 carbon atoms (unless specifically defined) that includes a straight chain alkyl or branched alkyl. The straight chain or branched lower alkyl group is chemically feasible and attached at any available point to provide a stable compound. In many embodiments, a lower alkyl is a straight or branched alkyl group containing from 1-6, 1-4, or 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like. A lower alkyl may be independently substituted as described herein, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, wherein the substituents are as indicated. For example "fluoro substituted lower alkyl" denotes a lower 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. It is understood that any such substitutions, or substitution of lower alkyl on another moiety, are chemically feasible and attached at any available atom to provide a stable compound.

[0122] "Alkylene" by itself or as part of another substituent means a linear or branched saturated divalent hydrocarbon radical derived from an alkane having the number of carbon atoms indicated in the prefix. For example, $(C_1$-$C_6)$alkylene is meant to include methylene,

ethylene, propylene, 2-methylpropylene, pentylene, hexylene, and the like. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10, 8, 6, 4 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 alkyl or alkylene portion, the radical or portion thereof will have 8 or fewer main chain carbon atoms or 6 or fewer main chain carbon atoms or 4 or fewer main chain carbon atoms.

[0123] "Lower alkenyl" alone or in combination means a straight or branched hydrocarbon containing 2-6 carbon atoms (unless specifically defined) and at least one, preferably 1-3, more preferably 1-2, most preferably one, carbon to carbon double bond. Carbon to carbon double bonds may be either contained within a straight chain or branched portion. The straight chain or branched lower alkenyl group is chemically feasible and attached at any available point to provide a stable compound. Examples of lower alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and the like. A "substituted lower alkenyl" denotes lower alkenyl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, wherein the substituents are as indicated. For example "lower alkenyl optionally substituted with $C(O)$-O-R^{28}" denotes a lower alkenyl group that may be substituted with a carboxylic acid moiety, i.e. $C(O)$-O-R^{28} is substituted on the alkenyl group, where the carbon of $C(O)$-O-R^{28} is bound to a carbon of the alkenyl group. It is understood that any such substitutions, or substitution of lower alkenyl on another moiety, are chemically feasible and attached at any available atom to provide a stable compound.

[0124] "Lower alkynyl" alone or in combination means a straight or branched hydrocarbon containing 2-6 carbon atoms (unless specifically defined) containing at least one, preferably one, carbon to carbon triple bond. The straight chain or branched lower alkynyl group is chemically feasible and attached at any available point to provide a stable compound. Examples of alkynyl groups include ethynyl, propynyl, butynyl, and the like. A "substituted lower alkynyl" denotes lower alkynyl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, wherein the substituents are as indicated. For example "lower alkynyl optionally substituted with R^{9}" denotes a lower alkynyl group that may be substituted with a substituent R^{9}. It is understood that any such substitutions, or substitution of lower alkynyl on another moiety, are chemically feasible and attached at any available atom to provide a stable compound.

[0125] "Cycloalkyl" refers to saturated or unsaturated, non-aromatic monocyclic carbon ring systems of 3-10, also 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclopentyl,

cyclohexyl, cycloheptyl, and the like. A "substituted cycloalkyl" is a cycloalkyl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, wherein the substituents are as indicated. It is understood that substitutions on cycloalkyl, or substitution of cycloalkyl on another moiety, are chemically feasible and attached at any available atom to provide a stable compound.

[0126] "Cycloalkylalkyl" refers to a -(alkylene)-R radical, where R is cycloalkyl as defined above, e. g., cyclopropylmethyl, cyclobutylethyl, cyclobutylmethyl, and the like.

[0127] "Heterocycloalkyl" refers to a saturated or unsaturated non-aromatic cycloalkyl group having from 5 to 10 atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N, and are optionally fused with benzo or heteroaryl of 5-6 ring members. Heterocycloalkyl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. Heterocycloalkyl is also intended to include compounds in which a ring carbon may be oxo substituted, i.e. the ring carbon is a carbonyl group, such as lactones and lactams. The point of attachment of the heterocycloalkyl ring is at a carbon or nitrogen atom such that a stable ring is retained. Examples of heterocycloalkyl groups include, but are not limited to, morpholino, tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, pyrrolidonyl, piperazinyl, dihydrobenzofuryl, dihydroindolyl, imidazolidinyl, pyrazolidinyl, butyrolactam radical, valerolactam radical, imidazolidinone radical, hydantoin, dioxolane radical, phthalimide radical, 1,4-dioxane radical, thiomorpholinyl, thiomorpholinyl-S-oxide, thiomorpholinyl-S,S-oxide, piperazinyl, pyranyl, 3-pyrrolinyl, thiopyranyl, pyrone radical, tetrahydrothiophenyl, quinuclidinyl, and the like. A "substituted heterocycloalkyl" is a heterocycloalkyl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, wherein the substituents are as indicated. It is understood that substitutions on heterocycloalkyl, or substitution of heterocycloalkyl on another moiety, are chemically feasible and attached at any available atom to provide a stable compound. "Heteroycloalkylalkyl" refers to a -(alkylene)-R radical, where R is heterocycloalkyl as defined herein.

[0128] "Aryl" alone or in combination refers to a monocyclic or bicyclic ring system containing aromatic hydrocarbons such as phenyl or naphthyl, which may be optionally fused with a cycloalkyl of preferably 5-7, more preferably 5-6, ring members. A "substituted aryl" is an aryl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, wherein the substituents are as indicated. It is understood that substitutions on aryl, or

substitution of aryl on another moiety, are chemically feasible and attached at any available atom to provide a stable compound.

[0129] "Aralkyl"refers to a -(alkylene)-R radical, where R is aryl as defined above e. g. , benzyl, phenethyl, and the like.

[0130] "Heteroaryl" alone or in combination 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 provided. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrazinyl, quinaoxalyl, indolizinyl, benzo[b]thienyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, pyrazolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazolyl, furanyl, benzofuryl, and indolyl. A "substituted heteroaryl" is a heteroaryl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, wherein the substituents are as indicated. It is understood that substitutions on heteroaryl, or substitution of heteroaryl on another moiety, are chemically feasible and attached at any available atom to provide a stable compound.

[0131] "Heteroarylalkyl" refers to a radical –(alkylene)-R, where R is a heteroaryl group as defined herein. Examples of heteroarylalkyl include 2-pyridylmethyl, 2-thiazolylethyl, 4H, 1,2,4-triazolyethyl, and the like.

[0132] "Lower alkoxy" denotes the group -OR^a, where R^a is lower alkyl. "Substituted lower alkoxy" denotes lower alkoxy in which R^a is lower alkyl substituted with one or more substituents as indicated herein. Preferably, substitution of lower alkoxy is with 1, 2, 3, 4, or 5 substituents, also 1, 2, or 3 substituents. For example "fluoro substituted lower alkoxy" denotes lower alkoxy in which the lower alkyl is substituted with one or more fluoro atoms, where preferably the lower alkoxy is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. It is understood that substitutions on alkoxy, or substitution of alkoxy on another moiety, are chemically feasible and attached at any available atom to provide a stable compound.

[0133] "Lower alkylthio" denotes the group -SR^b, where R^b is lower alkyl. "Substituted lower alkylthio" denotes lower alkylthio in which R^b is lower alkyl substituted with one or more substituents as

indicated herein. Preferably, substitution of lower alkylthio is with 1, 2, 3, 4, or 5 substituents, also 1, 2, or 3 substituents. For example "fluoro substituted lower alkylthio" denotes lower alkylthio in which the lower alkyl is substituted with one or more fluoro atoms, where preferably the lower alkylthio is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. It is understood that substitutions on alkylthio, or substitution of alkylthio on another moiety, are chemically feasible and attached at any available atom to provide a stable compound.

[0134] As used herein, "one or more substituents" specifically contemplates, inter alia, from one to seven, more preferably from one to five, even more preferably from one to three substituents on a particular group so as to satisfy the valence thereof. For example, the the number of substituents can be 1, 2, 3, 4, 5, 6 or 7.

[0135] "Mono-alkylamino" denotes the group -NHR^c where R^c is lower alkyl. "Di-alkylamino" denotes the group -NR^cR^d, where R^c and R^d are independently lower alkyl. "Cycloalkylamino" denotes the group -NR^eR^f, where R^e and R^f combine with the nitrogen to form a 5-7 membered heterocycloalkyl, where the heterocycloalkyl may contain an additional heteroatom within the ring, such as O, N, or S, and may also be further substituted with lower alkyl. Examples of 5-7 membered heterocycloalkyl include, but are not limited to, piperidine, piperazine, 4-methylpiperazine, morpholine, and thiomorpholine. It is understood that when mono-alkylamino, di-alkylamino, or cycloalkylamino are substituents on other moieties, these are chemically feasible and attached at any available atom to provide a stable compound.

[0136] As used herein "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), CURRENT PROTOCOLS IN NUCLEIC ACID CHEMISTRY, John Wiley and Sons, New York,Volume 1, 2000).

[0137] As used herein, the terms "treat", "treating", "therapy", "therapies", and like terms refer to the administration of material, e.g., any one or more compound(s) as described herein in an amount effective

to prevent, alleviate, or ameliorate one or more symptoms of a disease or condition, i.e., indication, and/or to prolong the survival of the subject being treated.

[0138] As used herein, the term "Raf protein kinase mediated disease or condition" refers to a disease or condition in which the biological function of a Raf protein kinase (also referred to as Raf kinase, or Raf), including any of A-Raf protein kinase, B-Raf protein kinase or c-Raf-1 protein kinase, or any mutation thereof, affects the development, course, and/or symptoms of the disease or condition, and/or in which modulation of Raf alters the development, course, and/or symptoms of the disease or condition. The Raf mediated disease or condition includes a disease or condition for which Raf modulation provides a therapeutic benefit, e.g. wherein treatment with Raf inhibitor(s), including one or more compound(s) described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition.

[0139] As used herein, the term "A-Raf protein kinase mediated disease or condition," and the like refer to a disease or condition in which the biological function of an A-Raf protein kinase (also referred to as A-Raf kinase, or A-Raf), including any mutations thereof, affects the development, course, and/or symptoms of the disease or condition, and/or in which modulation of A-Raf alters the development, course, and/or symptoms of the disease or condition. The A-Raf mediated disease or condition includes a disease or condition for which A-Raf inhibition provides a therapeutic benefit, e.g. wherein treatment with a compound that inhibits A-Raf, including one or more compound(s) described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition.

[0140] As used herein, the term "B-Raf protein kinase mediated disease or condition," and the like refer to a disease or condition in which the biological function of a B-Raf protein kinase (also referred to as B-Raf kinase, or B-Raf), including any mutations thereof, affects the development, course, and/or symptoms of the disease or condition, and/or in which modulation of B-Raf alters the development, course, and/or symptoms of the disease or condition. The B-Raf mediated disease or condition includes a disease or condition for which B-Raf inhibition provides a therapeutic benefit, e.g. wherein treatment with a compound that inhibits B-Raf, including one or more compound(s) described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition.

[0141] As used herein, the term "B-Raf V600E mutant protein kinase mediated disease or condition," and the like refer to a disease or condition in which the biological function of B-Raf V600E mutant protein kinase (also referred to as B-Raf V600E kinase, or B-Raf V600E) affects the development, course, and/or symptoms of the disease or condition, and/or in which modulation of B-Raf V600E alters the

development, course, and/or symptoms of the disease or condition. The B-Raf V600E mediated disease or condition includes a disease or condition for which B-Raf V600E inhibition provides a therapeutic benefit, e.g. wherein treatment with compound that inhibits B-Raf V600E, including one or more compound(s) described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition.

[0142] As used herein, the term "c-Raf-1 protein kinase mediated disease or condition," and the like refer to a disease or condition in which the biological function of a c-Raf-1 protein kinase (also referred to as c-Raf-1 kinase, or c-Raf-1), including any mutations thereof, affects the development, course, and/or symptoms of the disease or condition, and/or in which modulation of c-Raf-1 alters the development, course, and/or symptoms of the disease or condition. The c-Raf-1 mediated disease or condition includes a disease or condition for which c-Raf-1 inhibition provides a therapeutic benefit, e.g. wherein treatment with compound that inhibits c-Raf-1, including one or more compound(s) described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition.

[0143] As used herein, the term "Raf inhibitor" refers to a compound that inhibits at least one of A-Raf, B-Raf, c-Raf-1, or any mutations thereof, i.e. a compound having 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. Such compounds are preferably, but not necessarily, selective with respect to other protein kinases, i.e. when compared to another protein kinase, the IC_{50} for the other kinase divided by the IC_{50} for the Raf kinase is >10, also >20, also >30, also >40, also >50, also >60, also >70, also >80, also >90, also >100. Preferably, the compounds are selective relative to other protein kinases including, but not limited to, CSK, Insulin receptor kinase, AMPK, PDGFR or VEGFR.

[0144] As used herein, the term "c-Raf-1 inhibitor" refers to a compound that inhibits c-Raf-1 protein kinase, i.e. a compound having 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 c-Raf-1 kinase activity assay. Such compounds are effective in treating a disease or condition that is c-Raf-1 mediated. Such compounds are preferably, but not necessarily, selective with respect to other protein kinases, i.e. when compared to another protein kinase, the IC_{50} for the other kinase divided by the IC_{50} for c-Raf-1 kinase is >10, also >20, also >30, also >40, also >50, also >60, also >70, also >80, also >90, also >100. Preferably, the compounds are selective relative to other protein kinases including, but not limited to, CSK, Insulin receptor kinase, AMPK, PDGFR or VEGFR. Such compounds are preferably, but not

necessarily, also selective with respect to other Raf protein kinases, i.e. when compared to another Raf protein kinase, the IC_{50} for the other Raf kinase divided by the IC_{50} for c-Raf-1 kinase is >10, also >20, also >30, also >40, also >50, also >60, also >70, also >80, also >90, also >100. Preferably such compounds are at least selective relative to B-Raf and B-Raf V600E. While it is understood that a c-Raf-1 inhibitor may be used to treat any c-Raf-1 mediated disease or condition, the inihibition of c-Raf-1, preferably selective inhibition of c-Raf-1, provides beneficial effects in treating acute pain, chronic pain, and polycystic kidney disease.

[0145] As used herein, the term "B-Raf V600E inhibitor" refers to a compound that inhibits B-Raf V600E mutant protein kinase, i.e. a compound having 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 B-Raf V600E kinase activity assay. Such compounds are effective in treating a disease or condition that is B-Raf V600E mediated. Such compounds are preferably, but not necessarily, selective with respect to other protein kinases, i.e. when compared to another protein kinase, the IC_{50} for the other kinase divided by the IC_{50} for B-Raf V600E kinase is >10, also >20, also >30, also >40, also >50, also >60, also >70, also >80, also >90, also >100. Preferably, the compounds are selective relative to other protein kinases including, but not limited to, CSK, Insulin receptor kinase, AMPK, PDGFR or VEGFR. Such compounds are preferably, but not necessarily, also selective with respect to other Raf protein kinases, i.e. when compared to another Raf protein kinase, the IC_{50} for the other Raf kinase divided by the IC_{50} for B-Raf V600E kinase is >10, also >20, also >30, also >40, also >50, also >60, also >70, also >80, also >90, also >100. While it is understood that a B-Raf V600E inhibitor may be used to treat any B-Raf V600E mediated disease or condition, the inihibition of B-Raf V600E provides beneficial effects in treating 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.

[0146] As used herein, the term "pan Raf inhibitor" refers to a compound that inhibits at least each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases, i.e. a compound having an IC_{50} of 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, and having 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 comparable generally accepted c-Raf-1 kinase activity assay, and having 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 comparable generally accepted B-Raf V600E kinase activity assay. The pan Raf

inhibitor may be, but is not necessarily, approximately equipotent on each of B-Raf, c-Raf-1 and B-Raf V600E. Compounds are considered approximately equipotent on each of B-Raf V600E, B-Raf and c-Raf-1 if the ratio of IC_{50} for any of B-Raf V600E, B-Raf and c-Raf-1 divided by the IC_{50} for any other of B-Raf V600E, B-Raf and c-Raf-1 (e.g. B-Raf IC_{50} divided by B-Raf V600E IC_{50}) is in the range of 10 to 0.1, also 5 to 0.2. Such compounds are preferably, but not necessarily, selective with respect to other protein kinases, i.e. when compared to another protein kinase, the IC_{50} for the other kinase divided by the IC_{50} for any of B-Raf, c-Raf-1 or B-Raf V600E is >10, also >20, also >30, also >40, also >50, also >60, also >70, also >80, also >90, also >100. Preferably, the compounds are selective relative to other protein kinases including, but not limited to, CSK, Insulin receptor kinase, AMPK, PDGFR or VEGFR. While it is understood that a pan Raf inhibitor may be used to treat any B-Raf, c-Raf-1 or B-Raf V600E kinase mediated disease or condition, the inihibition of each of B-Raf, c-Raf-1 and B-Raf V600E provides beneficial effects in treating cancers, in particular cancers having a Ras pathway mutation, including, but not limited to, 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. Such compounds are also beneficial in treating B-Raf V600E mediated cancers that become resistant to B-Raf V600E selective inhibitors.

[0147] As used herein, the term "Ras activity inhibitor" refers to a compound that inhibits proliferation of a mutant Ras cell line; i.e., a compound that inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 1 μM, 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 1 μM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 100 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 50 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 20 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 10 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 5 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 1 nM. In some embodiments the mutant Ras cell line is a N-Ras mutant cell line, a K-Ras mutant cell line, or a H-Ras mutant cell line. In various embodiments a Ras activity inhibitor inhibits proliferation of a mutant N-Ras cell line with an IC_{50} of less than 1 μM, 100

nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a N-Ras mutant cell line with an IC_{50} of less than 1 μM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a N-Ras mutant cell line with an IC_{50} of less than 100 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a N-Ras mutant cell line with an IC_{50} of less than 50 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a N-Ras mutant cell line with an IC_{50} of less than 20 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a N-Ras mutant cell line with an IC_{50} of less than 10 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a N-Ras mutant cell line with an IC_{50} of less than 5 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a N-Ras mutant cell line with an IC_{50} of less than 1 nM. In certain embodiments, the N-Ras mutant cell line is one or more cell lines selected from the group consisting of M244, M202, M207, SK-MEL-2, IPC-298, S`117, M296, SK-MEL-30, SK-MEL-173, and HL-60. In some embodiments, the N-Ras mutant cell line is one or more cell lines selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298. In some embodiments, a Ras activity inhibitor inhibits proliferation of a mutant Ras cell line selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298 with an IC_{50} of less than 1 μM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a mutant Ras cell line selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298 with an IC_{50} of less than 100 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a mutant Ras cell line selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298 with an IC_{50} of less than 50 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a mutant Ras cell line selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298 with an IC_{50} of less than 20 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a mutant Ras cell line selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298 with an IC_{50} of less than 10 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a mutant Ras cell line selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298 with an IC_{50} of less than 5 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of a mutant Ras cell line selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298 with an IC_{50} of less than 1 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of IPC298 cells with an IC_{50} of less than 1 μM. In some embodiments, a Ras activity inhibitor inhibits proliferation of IPC298 cells with an IC_{50} of less than 100 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of IPC298 cells with an IC_{50} of less than 50 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of IPC298 cells with an IC_{50} of

less than 20 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of IPC298 cells with an IC_{50} of less than 10 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of IPC298 cells with an IC_{50} of less than 5 nM. In some embodiments, a Ras activity inhibitor inhibits proliferation of IPC298 cells with an IC_{50} of less than 1 nM.

[0148] As used herein, the term "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.

[0149] As used herein, the term "substantially crystalline" material embraces material which has greater than about 90% crystallinity; and "crystalline" material embraces material which has greater than about 98% crystallinity.

[0150] As used herein, the term "substantially amorphous" material embraces material which has no more than about 10% crystallinity; and "amorphous" material embraces material which has no more than about 2% crystallinity.

[0151] As used herein, the term "semi-crystalline" material embraces material which is greater than 10% crystallinity, but no greater than 90% crystallinity; preferably "semi-crystalline" material embraces material which is greater than 20% crystallinity, but no greater than 80% crystallinity. In one aspect of the present invention, a mixture of solid forms of a compound may be prepared, for example, a mixture of amorphous and crystalline solid forms, e.g. to provide a "semi-crystalline" solid form. Such a "semi-crystalline" solid form may be prepared by methods known in the art, for example by mixing an amorphous solid form with a crystalline solid form in the desired ratio. In some instances, a compound mixed with acid or base forms an amorphous complex; a semi-crystalline solid can be prepared employing an amount of compound component in excess of the stoichiometry of the compound and acid or base in the amorphous complex, thereby resulting in an amount of the amorphous complex that is based on the stoichiometry thereof, with excess compound in a crystalline form. The amount of excess compound used in the preparation of the complex can be adjusted to provide the desired ratio of amorphous complex to crystalline compound in the resulting mixture of solid forms. For example, where

the amorphous complex of acid or base and compound has a 1:1 stoichiometry, preparing said complex with a 2:1 mole ratio of compound to acid or base will result in a solid form of 50% amorphous complex and 50% crystalline compound. Such a mixture of solid forms may be beneficial as a drug product, for example, by providing an amorphous component having improved biopharmaceutical properties along with the crystalline component. The amorphous component would be more readily bioavailable while the crystalline component would have a delayed bioavailablity. Such a mixture may provide both rapid and extended exposure to the active compound.

[0152] As used herein, the term "complex" refers to a combination of a pharmaceutically active compound and an additional molecular species that forms or produces a new chemical species in a solid form. In some instances, the complex may be a salt, i.e. where the additional molecular species provides an acid/base counter ion to an acid/base group of the compound resulting in an acid:base interaction that forms a typical salt. While such salt forms are typically substantially crystalline, they can also be partially crystalline, substantially amorphous, or amorphous forms. In some instances, the additional molecular species, in combination with the pharmaceutically active compound, forms a non-salt co-crystal, i.e. the compound and molecular species do not interact by way of a typical acid:base interaction, but still form a substantially crystalline structure. Co-crystals may also be formed from a salt of the compound and an additional molecular species. In some instances, the complex is a substantially amorphous complex, which may contain salt-like acid:base interactions that do not form typical salt crystals, but instead form a substantially amorphous solid, i.e. a solid whose X-ray powder diffraction pattern exhibits no sharp peaks (e.g. exhibits an amorphous halo).

[0153] As used herein, the term "stoichiometry" refers to the molar ratio of a combination of two or more components, for example, the molar ratio of acid or base to compound that form an amorphous complex. For example, a 1:1 mixture of acid or base with compound (i.e. 1 mole acid or base per mole of compound) resulting in an amorphous solid form has a 1:1 stoichiometry.

[0154] As used herein, the term "composition" refers to a pharmaceutical preparation suitable for administration to an intended subject for therapeutic purposes that contains at least one pharmaceutically active compound, including any solid form thereof. The composition may include at least one pharmaceutically acceptable component to provide an improved formulation of the compound, such as a suitable carrier or excipient.

[0155] 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.

[0156] As used herein, the term "biopharmaceutical properties" refers to the pharmacokinetic action of a compound or complex of the present invention, including the dissolution, absorption and distribution of the compound on administration to a subject. As such, certain solid forms of compounds of the invention, such as amorphous complexes of compounds of the invention, are intended to provide improved dissolution and absorption of the active compound, which is typically reflected in improved C_{max} (i.e. the maximum achieved concentration in the plasma after administration of the drug) and improved AUC (i.e. area under the curve of drug plasma concentration vs. time after administration of the drug).

[0157] 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.

[0158] 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.

[0159] 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.

[0160] 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.

[0161] As used herein, the term "modulating" or "modulate" refers to an effect of altering a biological activity (i.e. increasing or decreasing the activity), especially a biological activity associated with a particular biomolecule such as a protein kinase. For example, an inhibitor of a particular biomolecule modulates the activity of that biomolecule, *e.g.*, an enzyme, by decreasing the activity of the biomolecule,

such as an enzyme. Such activity is typically indicated in terms of an inhibitory concentration (IC_{50}) of the compound for an inhibitor with respect to, for example, an enzyme.

[0162] 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.

[0163] "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.

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 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 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 mycloma. 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).

Kinase Activity Assays

[0173] 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.

[0174] Additional alternative assays can employ binding determinations. For example, this sort of assay can be formatted either in a fluorescence resonance energy transfer (FRET) format, or using an AlphaScreen (*a*mplified *l*uminescent *p*roximity *h*omogeneous *a*ssay) format by varying the donor and acceptor reagents that are attached to streptavidin or the phosphor-specific antibody.

Organic Synthetic Techniques

[0175] 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

[0176] 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

[0177] 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.

[0178] 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 7-position of the pyrrolo[2,3-d]pyrimidine ring, 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.

[0179] 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:

[0180] 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.

[0181] 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.

[0182] 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.

[0183] 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*.

[0184] 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.

[0185] 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

[0186] 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.

[0187] 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.

[0188] 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

[0189] Unless specified to the contrary, specification of a compound herein includes pharmaceutically acceptable salts of such compound. Thus, compounds described herein 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.

[0190] 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.

[0191] 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.

[0192] 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

[0193] 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.

[0194] 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.

[0195] 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.

Formulations and Administration

[0196] 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).

[0197] 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.

[0198] In some embodiments, oral administration may be used. Pharmaceutical preparations for oral use can be formulated into conventional oral dosage forms such as 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. 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.

[0199] 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.

[0200] 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.

[0201] 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.

[0202] 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.

[0203] 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.

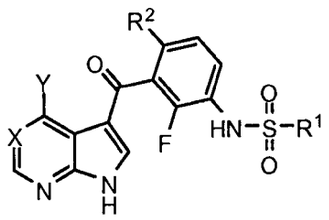
[0204] The compounds described herein may also be used in combination with other therapies for treating the same disease. Such combination use includes administration of the compounds and one or more other therapeutics at different times, or co-administration of the compound and one or more other therapies. 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.

[0205] 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.

[0206] In addition to the disclosures herein, the following non-limiting embodiments are contemplated herein:

1. A compound having the chemical structure of Formula I,



Formula I

or a pharmaceutically acceptable salt, hydrate or solvate thereof,

wherein:

X is –N= or –C(R^5)=;

Y is selected from the group consisting of fluoro, chloro, bromo, iodo, lower alkyl, lower alkoxy, haloalkyl, CN, -OH, cycloalkyl, -OR^8, and –N(R^3)(R^4); wherein:

R^3 is hydrogen and R^4 is selected from the group consisting of (i) hydrogen, -OR^8 and lower alkyl optionally substituted with one or more R^{11}; (ii) cycloalkyl or cycloalkylalkyl, each of which is optionally substituted with one or more R^{12}; (iii) heterocycloalkyl or heterocycloalkylalkyl, each of which is optionally substituted with one or more R^{13}; (iv) aryl or arylalkyl, each of which is optionally substituted with one or more R^{14}, optionally, wherein the two adjacent R^{14} groups on the aryl ring are taken together to form a 5 or 6-membered hetero cyclic aromatic ring having from 1-4 heteroatoms selected from O or N; and (v) heteroaryl or heteroarylalkyl, each of which is optionally substituted with one or more R^{15}; or

R^3 and R^4 are both lower alkyl; or

R^3 and R^4 combine with the nitrogen atom to which they are attached to form a 3-7 membered ring having 0-1 additional ring heteroatom selected from O, N or S, wherein the nitrogen or sulfur atom is optionally oxidized;

R^1 is selected from the group consisting of lower alkyl, haloalkyl, haloalkoxy, fluoro substituted lower alkyl, cycloalkyl optionally substituted with one or more R^7, heterocycloalkyl, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, aryl optionally substituted with one or more R^6 and heteroaryl optionally substituted with one or more R^7;

R^2 is hydrogen, fluoro, chloro, or lower alkyl optionally substituted with one or more fluorine;

R^5 is selected from the group consisting of hydrogen, fluoro, chloro, -CN, lower alkyl optionally substituted with one or more R^{16}, and lower alkoxy optionally substituted with one or more R^{17};

each R^6, when present, is independently selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, -C(O)-O-R^{15}, -N(H)-C(O)-R^{16}, and heteroaryl optionally substituted with one or more lower alkyl; or two R^5 on adjacent carbons combine to form a fused heterocycloalkyl optionally substituted with one or more lower alkyl;

each R^7, when present, is independently selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, lower alkoxy, -C(O)-O-R^{20}, and heteroaryl optionally substituted with one or more lower alkyl;

R^8 is hydrogen, lower alkyl optionally substituted with one or more fluorine, or, when R^8 is a C_{2-6} alkyl, said alkyl may optionally be substituted with one or more R^{21}; cycloalkyl optionally substituted with one or more R^{21}, or heterocycloalkyl optionally substituted with one or more R^{21};

each R^{11}, when present, is independently selected from the group consisting of fluoro, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, cycloalkyl optionally substituted with one or more R^{12}, heterocycloalkyl optionally substituted with one or more R^{13}, aryl optionally substituted with one or more R^{14}, and heteroaryl optionally substituted with one or more R^{15};

each R^{12}, when present, is independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, -N(H)-C(O)-R^{22}, -N(H)-$S(O)_2$-R^{23}, C(O)-R^{24}, and $S(O)_2$-R^{25};

each R^{13}, when present, is independently selected from the group consisting of fluoro, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino,

cycloalkylamino, heterocycloalkylamino, -N(H)-C(O)-R^{26}, -N(H)-$S(O)_2$-R^{27}, C(O)-R^{28}, $S(O)_2$-R^{29}, and lower alkyl optionally substituted with one or more R^{30};

each R^{14} and R^{15}, when present, are independently selected from the group consisting of fluoro, chloro, -OH, $-NH_2$, -CN, $-NO_2$, -N(H)-C(O)-R^{31}, -N(H)-$S(O)_2$-R^{32}, C(O)-R^{33}, $S(O)_2$-R^{34}, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, aryl optionally substituted with one or more R^{35}, and heteroaryl optionally substituted with one or more R^{36};

each R^{16}, when present, is independently fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{17}, when present, is independently fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{18} and R^{20}, when present, are independently hydrogen, lower alkyl or fluoro substituted lower alkyl;

each R^{19}, R^{22}, R^{23}, R^{26}, R^{27}, R^{31} and R^{32}, when present, are independently lower alkyl or fluoro substituted lower alkyl;

each R^{21}, when present, is fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{24}, R^{25}, R^{28}, R^{29}, R^{33}, and R^{34}, when present, are independently lower alkyl, fluoro substuted lower alkyl, -OH, lower alkoxy, fluor substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{30}, when present, is independently fluoro, aryl optionally substituted with one or more R^{35} or heteroaryl optionally substituted with one or more R^{36}; and

each R^{35} and R^{36}, when present, are independently selected from the group consisting of fluoro, chloro, -OH, $-NH_2$, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino.

2. The compound of embodiment **1**, wherein:

X is –N= or –C(R^5)=, wherein R^5 is selected from the group consisting of hydrogen, fluoro, chloro, -CN, lower alkyl and lower alkoxy, wherein the lower alkyl or lower alkoxy is optionally substituted with from one or three groups selected from fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

Y is selected from the group consisting of fluoro, chloro, bromo, iodo, lower alkyl, lower alkoxy, haloalkyl, CN, -OH, cycloalkyl, -OR^8, and –N(R^3)(R^4); wherein:

R^3 is hydrogen and R^4 is selected from the group consisting of (i) hydrogen, -OR^8 and lower alkyl optionally substituted with from one to three R^{11}; (ii) cycloalkyl or cycloalkylalkyl, each of which is optionally substituted with from one to three R^{12}; (iii) heterocycloalkyl or heterocycloalkylalkyl, each of which is optionally substituted with from one to three R^{13}; (iv) aryl or arylalkyl, each of which is optionally substituted with from one to three R^{14} optionally, wherein the two adjacent R^{14} groups on the aryl ring are taken together to form a 5 or 6-membered heterocyclic aromatic ring having from 1-4 heteroatoms selected from O or N; and (v) heteroaryl or heteroarylalkyl, each of which is optionally substituted with from one to three R^{15}; or

R^3 and R^4 are both lower alkyl; or

R^3 and R^4 are combined with the nitrogen atom to which they are attached to form a three to seven membered ring having 0-1 additional ring heteroatom selected from O, N or S, wherein the nitrogen or sulfur atom is optionally oxidized;

R^1 is selected from the group consisting of lower alkyl, haloalkyl, haloalkoxy, fluoro substituted lower alkyl, cycloalkyl optionally substituted with from one to three R^7, heterocycloalkyl, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, aryl optionally substituted with from one to three R^6 and heteroaryl optionally substituted with one to three R^7;

R^2 is hydrogen, fluoro, chloro, or lower alkyl optionally substituted with from one to five fluorine atoms;

each R^6, when present, is independently selected from the group consisting of fluoro, chloro, -CN, -NO_2, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, -C(O)-O-R^{15}, -N(H)-C(O)-R^{16}, and heteroaryl optionally substituted with one or more lower alkyl; or two R^5 on adjacent carbons combine to form a fused heterocycloalkyl optionally substituted with one or more lower alkyl;

each R^7, when present, is independently selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, lower alkoxy, -C(O)-O-R^{20}, and heteroaryl optionally substituted with one or more lower alkyl;

R^8 is hydrogen, lower alkyl optionally substituted with one or more fluorine, or, when R^8 is a C_{2-6} alkyl, said alkyl may optionally be substituted with one or more R^{21}; cycloalkyl optionally substituted with one or more R^{21}, or heterocycloalkyl optionally substituted with one or more R^{21};

each R^{11}, when present, is independently selected from the group consisting of fluoro, -OH, lower alkoxy, fluoro substituted lower alkoxy, -NH_2, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, cycloalkyl optionally substituted with one or more R^{12},

heterocycloalkyl optionally substituted with one or more R^{13}, aryl optionally substituted with one or more R^{14}, and heteroaryl optionally substituted with one or more R^{15};

each R^{12}, when present, is independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, $-N(H)-C(O)-R^{22}$, $-N(H)-S(O)_2-R^{23}$, $C(O)-R^{24}$, and $S(O)_2-R^{25}$;

each R^{13}, when present, is independently selected from the group consisting of fluoro, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, $-N(H)-C(O)-R^{26}$, $-N(H)-S(O)_2-R^{27}$, $C(O)-R^{28}$, $S(O)_2-R^{29}$, and lower alkyl optionally substituted with one or more R^{30};

each R^{14} and R^{15}, when present, are independently selected from the group consisting of fluoro, chloro, -OH, $-NH_2$, -CN, $-NO_2$, $-N(H)-C(O)-R^{31}$, $-N(H)-S(O)_2-R^{32}$, $C(O)-R^{33}$, $S(O)_2-R^{34}$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, aryl optionally substituted with one to three R^{35}, and heteroaryl optionally substituted with one to three R^{36};

each R^{18} and R^{20}, when present, are independently hydrogen, lower alkyl or fluoro substituted lower alkyl;

each R^{19}, R^{22}, R^{23}, R^{26}, R^{27}, R^{31} and R^{32}, when present, are independently lower alkyl or fluoro substituted lower alkyl;

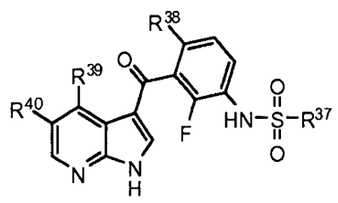
each R^{21}, when present, is fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{24}, R^{25}, R^{28}, R^{29}, R^{33}, and R^{34}, when present, are independently lower alkyl, fluoro substuted lower alkyl, -OH, lower alkoxy, fluor substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{30}, when present, is independently fluoro, aryl optionally substituted with one or more R^{35} or heteroaryl optionally substituted with one to three R^{36}; and

each R^{35} and R^{36}, when present, are independently selected from the group consisting of fluoro, chloro, -OH, $-NH_2$, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino.

3. The compound of embodiment **1** or **2**, having Formula II:



II

wherein:

R^{37} is selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, cycloalkyl, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, phenyl optionally substituted with one or more R^{41} and heteroaryl optionally substituted with one or more R^{42};

R^{38} is hydrogen, fluoro, chloro, or lower alkyl optionally substituted with one or more fluorine;

R^{39} and R^{40} are each independently selected from the group consisting of fluoro, chloro, -CN, -OH, $-NH_2$, lower alkoxy, lower alkyl optionally substituted with one or more R^{43}, lower alkenyl optionally substituted with C(O)-O-R^{44}, lower alkynyl optionally substituted with lower alkyl optionally substituted with one or more fluorine, or, on a non-alkynyl carbon thereof, R^{45}, lower alkoxy optionally substituted with R^{46}, mono-alkylamino, di-alkylamino, cycloalkylamino, cycloalkylalkyl-NH-, heterocycloalkylamino and heterocycloalkylalkyl-NH-;

each R^{41}, when present, is independently selected from the group consisting of halogen, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, -C(O)-O-R^{47}, -N(H)-C(O)-R^{48}, and heteroaryl optionally substituted with one or more lower alkyl; or two R^{41} on adjacent carbons combine to form a fused heterocycloalkyl optionally substituted with one or more lower alkyl;

each R^{42}, when present, is independently selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, -C(O)-O-R^{49}, and heteroaryl optionally substituted with one or more lower alkyl;

each R^{43}, when present, is independently selected from the group consisting of fluoro, -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino;

each R^{44}, when present, is independently hydrogen or lower alkyl optionally substituted with one or more fluorine;

each R^{45}, when present, is independently selected from the group consisting of -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino;

each R^{46}, when present, is independently selected from the group consisting of -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino;

each R^{47}, when present, is independently hydrogen or lower alkyl optionally substituted with one or more fluorine;

each R^{48}, when present, is independently lower alkyl optionally substituted with one or more fluorine; and

each R^{49}, when present, is independently hydrogen or lower alkyl optionally substituted with one or more fluorine.

4. The compound of embodiment **3**, wherein R^{37} is lower alkyl, fluoro substituted lower alkyl or phenyl, optionally substituted with from 1-3 R^{41} groups.

5. The compound of embodiment **4**, wherein R^{37} is lower alkyl, fluoro substituted lower alkyl or phenyl substituted with from 1-3 groups selected from fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, $-C(O)-O-R^{47}$ or $-N(H)-C(O)-R^{48}$.

6. The compound of embodiment **5**, wherein R^{37} is lower alkyl or phenyl substituted with from 1-2 groups selected from fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy or fluoro substituted lower alkoxy.

7. The compound of embodiment **3**, wherein R^{38} is H, -F or fluoro substituted lower alkyl.

8. The compound of embodiment **3**, wherein R^{39} is fluoro, chloro, -CN, -OH, $-NH_2$, lower alkoxy, lower alkyl optionally substituted with one or more R^{43}, cycloalkylamino, cycloalkylalkyl-NH-, heterocycloalkylamino and heterocycloalkylalkyl-NH-.

9. The compound of embodiment **3**, wherein R^{40} is H, lower alkyl optionally substituted with one or more R^{43}, halogen, lower alkoxy or –CN.

10. The compound of any of embodiments **3-9,** wherein R^{37} is lower alkyl or phenyl optionally substituted with 1-2 members selected from CF_3 or halogen.

11. The compound of embodiment **10**, wherein R^{37} is propyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl or 2,5-difluoro-substituted phenyl.

12. The compound of embodiment **11**, wherein R^{37} is propyl, 4-trifluoromethylphenyl, 2-fluorophenyl, 3-fluorophenyl or 2,5-difluoro-substituted phenyl.

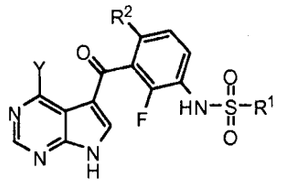
13. The compound of any of embodiments **3-9,** wherein R^{38} is H, F or CF_3.

14. The compound of any of embodiments **3-9**, wherein R^{38} is F.

15. The compound of any of embodiments **3-9,** wherein R^{39} is fluoro, chloro, -CN, -OH, $-NH_2$, lower alkyl optionally substituted with fluoro, lower alkoxy, cycloalkylamino, cycloalkylalkyl-NH-, heterocycloalkylamino and heterocycloalkylalkyl-NH-.

16. The compound of embodiment **15**, wherein R^{39} is fluoro, chloro, -CN, -OH, $-NH_2$, CH_3, CH_3O-, CF_3, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cyclopropylmethylamino, cyclobutylmethylamino, cyclopentylmethylamino, cyclohexylmethylamino, 2-tetrahydrofuranylamino, 3-tetrahydrofuranylamino or 4-tetrahydropyranylamino.

17. The compound of embodiment **1** or **2**, having Formula III:



III

18. The compound of any of embodiments **1, 2** or **17**, wherein X is selected from the group consisting of –N=, –CH=, -C(CH_3)=, -C(OCH_3)=, -C(F)=, -C(CN)=, -C(CH_2OH)= and –C(Cl)=.

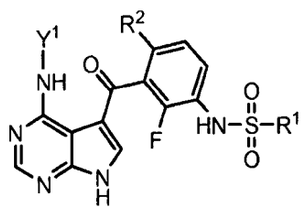
19. The compound of any of embodiments **1, 2** or **17**, wherein X is –N=, –CH=, -C(CH_3)=, -C(F)= or -C(CN)=.

20. The compound of any of embodiments **1, 2** or **17**, wherein X is –N=.

21. The compound of any of embodiments **1, 2** or **17**, wherein Y is fluoro, chloro, bromo, iodo, lower alkyl, lower alkoxy, haloalkyl, CN, -OH, cycloalkyl, -OR^8 or –NH(R^4).

22. The compound of any of embodiments **1, 2** or **17**, wherein Y is CH_3, ethyl, methoxy, ethyoxy, isobutyl, CN, OH, F, Cl, Br, I, NH_2, butyoxy, 2-methylpropoxy, 4-tetrahydropyranyloxy, 2-tetrahyrofuranyloxy, 3-tetrahyrofuranyloxy, alkoxyamino or HO-NH-.

23. The compound of embodiments **1** or **2**, having Formula IIIa:



IIIa

wherein Y^1 is lower alkyl optionally substituted with from one to three R^{11}, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, wherein:

(i) the cycloalkyl and cycloalkylalkyl are each optionally substituted with from one to three R^{12};

(ii) the heterocycloalkyl and heterocycloalkylalkyl are each optionally substituted with from one to three R^{13};

(iii) the aryl and arylalkyl are each optionally substituted with from one to three R^{14} optionally, wherein the two adjacent R^{14} groups on the aryl ring are taken together to form a 5 or 6-membered hetero aromatic ring having from 1-4 heteroatoms selected from O or N; and

(iv) the heteroaryl and heteroarylalkyl are each optionally substituted with from one to three R^{15}.

24. The compound of embodiment **23**, wherein Y^1 is selected from lower alkyl, halogen substituted lower alkyl, 2-hydroxyethyl, cyclopropylamino, cyclobutyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexyl, 2-oxetanyl, 2-oxetanylmethyl, 3-oxetanyl, 3-oxetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 2-tetrahydropyranylmethyl, 3-tetrahydropyranylmethyl, 4-tetrahydropyranylmethyl, 1-methyl-2-aziridinyl, 1-methyl-2-aziridinylmethyl, 1-methyl-2-azetidinyl, 1-methyl-2-azetidinylmethyl, 1-methyl-3-azetidinyl, 1-methyl-3-azetidinylmethyl, 1-methyl-2-pyrrolidinyl, 1-methyl-2-pyrrolidinylmethyl, 1-methyl-3-pyrrolidinyl, 1-methyl-3-pyrrolidinylmethyl, 1-methyl-2-piperidinyl, 1-methyl-2-piperidinylmethyl, 1-methyl-3-piperidinyl, 1-methyl-3-piperidinylmethyl, 1-methyl-4-piperidinyl, 1-methyl-4-piperidinylmethyl, 1-methylsulfonyl-2-piperidinyl, 1-methylsulfonyl-2-piperidinylmethyl, 1-methylsulfonyl-3-piperidinyl, 1-methylsulfonyl-3-piperidinylmethyl, 1-methylsulfonyl-4-piperidinyl, 1-methylsulfonyl-4-piperidinylmethyl, 1,1-dioxo-4-thianyl, 1,1-dioxo-4-thianylmethyl, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-benzyl, 2-fluorobenzyl, 3-

fluorobenzyl, 4-fluorobenzyl, 2-pyridyl, 2-pyridylmethyl, 3-pyridyl, 3-pyridylmethyl, 4-pyridyl, 4-pyridylmethyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-dimethylaminophenyl, 3-dimethylaminophenyl, 4-dimethylaminophenyl, 2-dimethylaminobenzyl, 2-dimethylaminobenzyl, 3-dimethylaminobenzyl, 4-dimethylaminobenzyl, 2-hydoxyphenyl, 3-hydoxyphenyl, 4-hydoxyphenyl, 2-hydroxybenzyl, 3-hydroxybenzyl, 4-hydroxybenzyl, 2-carboxyphenyl, 3-carboxyphenyl, 4-carboxyphenyl, 2-carboxybenzyl, 3-carboxybenzyl, 4-carboxybenzyl, 2-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methoxycarbonylphenyl, 2-methoxycarbonylbenzyl, 3-methoxycarbonylbenzyl, 4-methoxycarbonylbenzyl, 1-alkyl-4-pyrazolyl, 1-alkyl-4-pyrazolylmethyl, 3-pyridazinyl, pyridazinylmethyl, 4-pyridazinyl, 4-pyridazinylmethyl, triazolyl, triazolymethyl, tetrazolyl, tetrazolymethyl, 2,1,3,-benzoxadiazolyl, 2,1,3-benzoxadiazol-5-yl, 2,1,3,-benzoxadiazolyl-methyl, 2,1,3-benzoxadiazol-5ylmethyl, 2,1,3,-benzothiadiazolyl, 2,1,3-benzothiadiazol-5-yl, 2,1,3,-benzothiadiazolyl-methyl, 2,1,3-benzothiadiazol-5ylmethyl, 1H-1,2,4-triazol-5-yl, 1H-1,2,4-triazol-5-methyl, 2-oxobenzimidazol-4-yl, 2-oxobenzimidazol-4-methyl, 2-oxobenzimidazol-5-yl, 2-oxobenzimidazol-5-methyl, 1,1,-dioxo-thiolan-3-yl, 1,1-dioxothiolan-3-methyl, 3-(2-methyl-1,2,3,4-tetrazol-5-yl)phenyl, 3-(2-methyl-1,2,3,4-tetrazol-5-yl)benzyl, 3-(5-methyl-1,2,3,4-tetrazol-1-yl)phenyl, 3-(1,2,4-triazol-5-yl)phenyl, 3-(1,2,,4-triazol-5-yl)benzyl, 3-3-methyl-4H-1,2,4-triazol-5-methyl or 2-(3-methyl-4H-1,2,4-triazol-5-yl)ethyl.

25. The compound of any of embodiments **17-23** or **24**, wherein R^2 is H or F.

26. The compound of any of embodiments **17-23** or **24**, wherein R^1 is lower alkyl, cycloalkyl optionally substituted with 1-2 groups selected from halogen or lower alkyl, heterocycloalkyl, heteroaryl optionally substituted with lower alkyl or lower alkoxy, phenyl optionally subtitued with 1-2 substitutents selected from lower alkyl, halogen, lower alkoxy, haloalkyl, haloalkoxy or CN.

27. The compound of embodiment **26**, wherein R^1 is methyl, propyl, isobutyl, 2-methylpropyl, CF_3, CF_3CH_2-, CHF_2CH_2-, 4-trifluorophenyl, 2-trifluorophenyl, 3-trifluorophenyl, 3,5-dimethylphenyl, 4-propylphenyl, 3-fluoro-4-methoxyphenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-fluoro-3-methoxyphenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,4-difluorophenyl, 2-pyridyl, 3-pyridyl, 5-methoxy-2-pyridyl, 3-methoxy-2-pyridyl, 4-methoxy-2-pyridyl, 6-methyl-2-pyridyl, 5-methyl-2-pyridyl, 4-methyl-2-pyridyl, 3-methyl-2-pyridyl, dialkylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, cycloprpyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-difluorocyclohexyl, 1-methyl-4-pyrazolyl, 1-ethyl-4-pyrazolyl, 1-methyl-3-pyrazolyl, 1-ethyl-3-pyrazolyl, 6-methyl-3-pyridyl, 5-methyl-3-pyridyl, 4-methyl-3-pyridyl or 2-methyl-3-pyridyl.

28. The compound of embodiment **27**, wherein R^1 is 2-fluorophenyl, 3-fluorophenyl, 2,5-difluorophenyl or 4-lower alkyl-substituted phenyl, wherein lower alkyl is optionally substituted with one or more fluorine.

29. The compound of any of embodiments **17-22**, wherein Y is $-NR^3R^4$, wherein R^3 and R^4 are combined with the nitrogen atom to which they are attached to form a three to seven membered ring having 0-1 additional heteroatom selected from O, N or S, wherein the nitrogen and sulfur atoms are optionally oxidized.

30. The compound of embodiment **29**, wherein Y is 1-aziridinyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl or 1-azepanyl.

31. A compound selected from the group consisting of:
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1001**),
Propane-1-sulfonic acid [3-(4-ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1002**),
2-Methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1003**),
2-Methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1004**),
N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1005**),
N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1006**),
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1007**),
N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide (**P-1008**),
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1009**),
N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1010**),
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-

benzenesulfonamide (**P-1012**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1014**),

N-[2,4-Difluoro-3-(4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1015**),

N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1016**),

6-Methoxy-pyridine-3-sulfonic acid [2,4-difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1018**),

N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide (**P-1019**),

N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1021**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1022**),

N-[3-(4-Cyano-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1023**),

N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3,5-dimethyl-benzenesulfonamide (**P-1025**),

N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3,5-dimethyl-benzenesulfonamide (**P-1027**),

N-[2,4-Difluoro-3-(4-isobutoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1028**),

N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1029**),

N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1030**),

Propane-1-sulfonic acid [3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1033**),

N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1034**),

N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-fluoro-4-methoxy-benzenesulfonamide (**P-1036**),

N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1038**),
N-[3-(4-Cyclopropylmethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1053**),
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1070**),
N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1071**),
N-[3-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1107**),
N-[3-(4-Cyclopropylmethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1181**),
N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1182**),
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1183**),
N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1184**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-2015**),
N-[2,4-Difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2016**),
N-[2,4-Difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide (**P-2017**), and
any pharmaceutically acceptable salt thereof.

32. A composition comprising a compound of any of embodiments **1-31** and a pharmaceutically acceptable excipient or carrier.

33. A pharmaceutical composition comprising a compound of any of embodiments **1-31** and another drug.

34. A kit comprising a compound according to any of embodiments **1-31** or a composition according to Embodiment **32** or **33**.

35. A method for treating a Raf protein kinase mediated disease or condition in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of embodiments **1-31** or a composition of embodiments **32** or **33.**

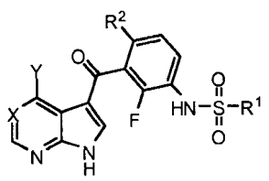
36. A method for treating a Raf protein kinase mediated disease or condition in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of embodiments **1-31** and another drug or a pharmaceutically acceptable salt thereof.

37. The method of embodiment **35** or **36,** wherein the disease or condition is selected from the group consisting of 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).

38. The method of embodiment **37** wherein 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, testicular cancer, and cholangiocarcinoma.

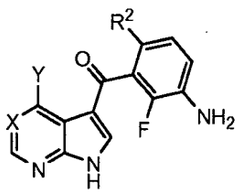
39. A method for preparing a compound of Formula I according to embodiment **1**



I

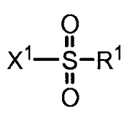
said method comprising:

contacting a compound of Formula IVc:



IVc

with a compound of Formula V:



V

under conditions sufficient to form the compound of Formula I, wherein:

X^1 is a halogen.

40. The method of embodiment **39**, wherein X is –N=, –CH=, -C(CH_3)=, -C(OCH_3)=, -C(F)=, -C(CN)=, -C(CH_2OH)= or –C(Cl)=.

41. Use of a compound according to any one of Embodiments **1-31** or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating any Raf protein kinase mediated disease or condition in a subject in need thereof.

42. A compound according to any one of Embodiments **1-31** or a composition according to any one of Embodiments **32** or **33** for use in treating of a Raf protein kinase mediated disease or condition in a subject in need thereof.

43. A method for treating one or more indications 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, testicular cancer, and cholangiocarcinoma in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

44. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating one or more indications 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, testicular cancer, and cholangiocarcinoma in a subject in need thereof.

45. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33**for the treatment of one or more indications 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, testicular cancer, and cholangiocarcinoma in a subject in need thereof.

46. A method for treating melanoma in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

47. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating melanoma in a subject in need thereof.

48. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33**for the treatment melanoma in a subject in need thereof.

49. A method for treating glioma in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

50. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating glioma in a subject in need thereof.

51. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for glioma in a subject in need thereof.

52. A method for treating glioblastoma multiforme in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

53. Use of a compound according to any one of **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33**for the preparation of a medicament for treating glioblastoma multiforme in a subject in need thereof.

54. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33**for the treatment of glioblastoma multiforme in a subject in need thereof.

55. A method for treating pilocytic astrocytoma, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

56. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating pilocytic astrocytoma in a subject in need thereof.

57. A compound according to any one of Embodiments **11-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the treatment of pilocytic astrocytoma in a subject in need thereof.

58. A method for treating colorectal cancer comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

59. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33**for the preparation of a medicament for treating colorectal cancer in a subject in need thereof.

60. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33**for the treatment of colorectal cancer in a subject in need thereof.

61. A method for treating thyroid cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

62. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating thyroid cancer in a subject in need thereof.

63. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the treatment of thyroid cancer in a subject in need thereof.

64. A method for treating, lung cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

65. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating lung cancer in a subject in need thereof.

66. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33**for the treatment of lung cancer in a subject in need thereof.

67. A method for treating ovarian cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

68. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33**for the preparation of a medicament for treating ovarian cancer in a subject in need thereof.

69. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the treatment of ovarian cancer in a subject in need thereof.

70. A method for treating prostate cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

71. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating prostate cancer in a subject in need thereof.

72. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the treatment of prostate cancer in a subject in need thereof.

73. A method for treating liver cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

74. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating liver cancer in a subject in need thereof.

75. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the treatment of liver cancer in a subject in need thereof.

76. A method for treating gallbladder cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-**

31, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments 32 or 33.

77. Use of a compound according to any one of Embodiments 1-31, a compound listed on Table I or Table II, or a composition according to any one of Embodiments 32 or 33 for the preparation of a medicament for treating gallbladder cancer in a subject in need thereof.

78. A compound according to any one of Embodiments 1-31, a compound listed on Table I or Table II, or a composition according to any one of Embodiments 32 or 33 for the treatment of gallbladder cancer in a subject in need thereof.

79. A method for treating gastrointestinal stromal tumors in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments 1-31, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments 32 or 33.

80. Use of a compound according to any one of Embodiments 1-31, a compound listed on Table I or Table II, or a composition according to any one of Embodiments 32 or 33 for the preparation of a medicament for treating gastrointestinal stromal tumors in a subject in need thereof.

81. A compound according to any one of Embodiments 1-31, a compound listed on Table I or Table II, or a composition according to any one of Embodiments 32 or 33 for the treatment of gastrointestinal stromal tumors in a subject in need thereof.

82. A method for treating biliary tract cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments 1-31, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments 32 or 33.

83. Use of a compound according to any one of Embodiments 1-31, a compound listed on Table I or Table II, or a composition according to any one of Embodiments 32 or 33 for the preparation of a medicament for treating biliary tract cancer in a subject in need thereof.

84. A compound according to any one of Embodiments 1-31, a compound listed on Table I or Table II, or a composition according to any one of Embodiments 32 or 33 for the treatment of biliary tract cancer in a subject in need thereof.

85. A method for treating cholangiocarcinoma in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

86. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating cholangiocarcinoma in a subject in need thereof.

87. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the treatment of cholangiocarcinoma in a subject in need thereof.

88. A method for treating one or more indications selected from the group consisiting of acute pain, chronic pain, and polycystic kindney disease in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

89. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating one or more indications selected from the group consisting of acute pain, chronic pain, and polycystic kindney disease in a subject in need thereof.

90. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the treatment of one or more indications selected from the group consisting of acute pain, chronic pain, and polycystic kindney disease in a subject in need thereof.

91. A method for treating acute pain in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

92. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating acute pain in a subject in need thereof.

93. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the treatment of acute pain in a subject in need thereof.

94. A method for treating chronic pain in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

95. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating chronic pain in a subject in need thereof.

96. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the treatment of chronic pain in a subject in need thereof.

97. A method for treating polycystic kindney disease in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

98. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating polycystic kindney disease in a subject in need thereof.

99. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the treatment of polycystic kindney disease in a subject in need thereof.

100. A method for treating one or more indications selected from the group consisiting of 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 a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

101. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating one or more indications selected from the group consisting of 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 a subject in need thereof.

102. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the treatment of one or more indications selected from the group consisting of 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 a subject in need thereof.

103. A method for treating testicular cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33.**

104. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating testicular cancer in a subject in need thereof.

105. A compound according to any one of Embodiments **11-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the treatment of testicular cancer in a subject in need thereof.

106. A method for treating Noonan's syndrome in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

107. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the preparation of a medicament for treating Noonan's syndrome in a subject in need thereof.

108. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the treatment of Noonan's syndrome in a subject in need thereof.

109. A method for treating cardio-faciocutaneous syndrome (CFC) in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or an effective amount of a composition according to any one of Embodiments **32** or **33**.

110. Use of a compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33**for the preparation of a medicament for treating cardio-faciocutaneous syndrome (CFC) in a subject in need thereof.

111. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** for the treatment of cardio-faciocutaneous syndrome (CFC) in a subject in need thereof.

112. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** wherein said compound is a pan Raf inhibitor.

113. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** wherein said compound is a Ras activity inhibitor.

114. A compound according to any one of Embodiments **1-31**, a compound listed on Table I or Table II, or a composition according to any one of Embodiments **32** or **33** wherein said compound is a pan Raf inhibitor and a Ras activity inhibitor.

115. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 1 μM.

116. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 100 nM.

117. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 20 nM.

118. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 1 nM.

119. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 1 μM and wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

120. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 100 nM and wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

121. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 20 nM and wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

122. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line with an IC_{50} of less than 1 nM and wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

123. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a N-Ras mutant cell line with an IC_{50} of less than 1 μM.

124. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a a N-Ras mutant cell line with an IC_{50} of less than 100 nM.

125. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a a N-Ras mutant cell line with an IC_{50} of less than 20 nM.

126. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a a N-Ras mutant cell line with an IC_{50} of less than 1 nM.

127. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a a N-Ras mutant cell line with an IC_{50} of less than 1 μM and wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

128. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a a N-Ras mutant cell line with an IC_{50} of less than 100 nM and wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

129. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a a N-Ras mutant cell line with an IC_{50} of less than 20 nM and wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

120. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a a N-Ras mutant cell line with an IC_{50} of less than 1 nM and wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

121. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298 with an IC_{50} of less than 1 μM.

122. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298 with an IC_{50} of less than 100 nM.

123. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298 with an IC_{50} of less than 20 nM.

124. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298 with an IC_{50} of less than 1 nM.

125. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298 with an IC_{50} of less than 1 μM and wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

126. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298 with an IC_{50} of less than 100 nM and

wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

127. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298 with an IC_{50} of less than 20 nM and wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

128. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of a mutant Ras cell line selected from the group consisting of M244, M202, M207, SK-MEL-2, SK-MEL-173, and IPC298 with an IC_{50} of less than 1 nM and wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

129. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of IPC298 cells with an IC_{50} of less than 1 μM.

130. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of IPC298 cells with an IC_{50} of less than 100 nM.

131. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of IPC298 cells with an IC_{50} of less than 20 nM.

132. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of IPC298 cells with an IC_{50} of less than 1 nM.

133. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of IPC298 cells with an IC_{50} of less than 1 μM and wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

134. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of IPC298 cells with an IC_{50} of less than 100 nM and wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

135. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of IPC298 cells with an IC_{50} of less than 20 nM and wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

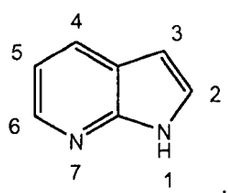
136. A compound or composition according to any one of the preceeding embodiments, wherein said compound inhibits proliferation of IPC298 cells with an IC_{50} of less than 1 nM and wherein said compound is a pan Raf inhibitor having an IC_{50} of less than 500 nM in activity assays for each of B-Raf, c-Raf-1 and B-Raf V600E protein kinases.

EXAMPLES

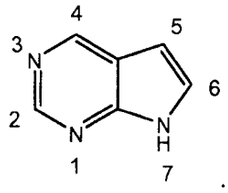
[0207] Examples related to the present invention are described below. In most cases, alternative techniques can be used. The examples are intended to be illustrative and are not limiting or restrictive to the scope of the invention. For example, where additional compounds are prepared following a protocol of a Scheme for a particular compound, it is understood that conditions may vary, for example, any of the solvents, reaction times, reagents, temperatures, work up conditions, or other reaction parameters may be varied employing alternate solvents, reagents, reaction times, temperatures, work up conditions, and the like, as are readily available to one skilled in the art. 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.

[0208] Unless specifically indicated otherwise, the Formula enumeration and R group enumeration used in the following examples is not related to such enumeration in other sections of this application. The reagents and solvents used in these examples can be readily substituted with appropriate alternatives as are known in the art and isolation of products is readily achieved by methods known in the art, including, but not limited to, extraction, crystallization, and chromatographic methods.

[0209] Ring numbering for the 1H-pyrrolo[2,3-b]pyridine in the following Examples is as follows:



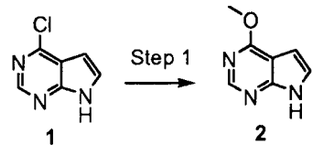
[0210] Ring numbering for the 7H-pyrrolo[2,3-d]pyrimidine in the following Examples is as follows:



Example 1: Synthesis of 7H-pyrrolo[2,3-d]pyrimidine compounds.

[0211] 4-methoxy-7H-pyrrolo[2,3-d]pyrimidine **2** is prepared in one step from 4-chloro-7H-pyrrolo[2,3-d]pyrimidine **1** as shown in Scheme 1.

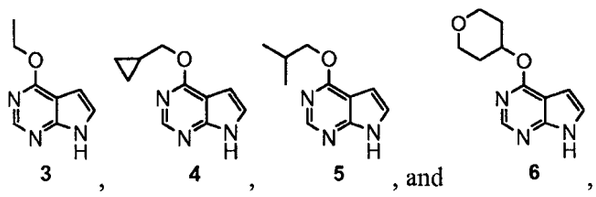
Scheme 1



Step 1 – Preparation of 4-methoxy-7H-pyrrolo[2,3-d]pyrimidine (2):

[0212] To 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**1**, 3.5 g, 23.0 mmol) in 70 mL of methanol, potassium hydroxide (2.3 g, 41.0 mmol) is added and the reaction stirred at 60 °C overnight, then poured into water and extracted with ethyl acetate. The organic layer is separated and dried over sodium sulfate, filtered and the filtrate concentrated under vacuum to provide the desired compound (**2**, 3.20 g).

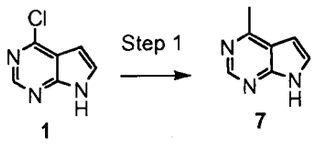
[0213] 4-ethoxy-7H-pyrrolo[2,3-d]pyrimidine **3**, 4-cyclopropylmethoxy-7H-pyrrolo[2,3-d]pyrimidine **4**, 4-isobutoxy-7H-pyrrolo[2,3-d]pyrimidine **5**, and 4-(tetrahydro-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidine **6**,



are prepared following the protocol of Scheme 1, replacing methanol with ethanol, cyclopropyl-methanol, isobutyl alcohol, and tetrahydro-pyran-4-ol, respectively. MS (ESI) $[M+H^+]^+$ = 164.9 (**3**); 190.1 (**4**); 192.1 (**5**); and 220.1 (**6**).

[0214] 4-Methyl-7H-pyrrolo[2,3-d]pyrimidine **7** is synthesized in one step from 4-chloro-7H-pyrrolo[2,3-d]pyrimidine **1** as shown in Scheme 1a.

Scheme 1a

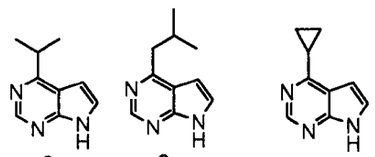


1 **7**

Step 1 – Preparation of 4-methyl-7H-pyrrolo[2,3-d]pyrimidine (7):

[0215] Into a round bottom flask the catalyst [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), 1:1 complex with dichloromethane (70.0 mg, 0.09 mmol), is placed under nitrogen with 15 mL of toluene along with a stir bar. A suspension of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**1**, 1.47 g, 9.57 mmol) in 15 mL of toluene is added at room temperature. After stirring for 10 minutes, methylmagnesium bromide (17.00 mL, 3.00 M in ether, 51.00 mmol) is added dropwise. The solution is slowly heated to 60 °C and stirred for 3 hrs at 60 °C, then overnight at room temperature. The resulting dark orange reaction mixture is quenched with 1 N hydrochloric acid and adjusted to pH ~5, then extracted with ethyl acetate and water saturated with sodium chloride. The organic layer is washed with water and brine, dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with ethyl acetate and hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound as a yellow solid (**8**, 202 mg). ^{1}H-NMR(dmso-d6) is consistent with the desired compound. MS(ESI) $[M+H^+]^+$ = 134.3.

[0216] 4-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine **8**, 4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine **9**, and 4-cyclopropyl-1H-pyrrolo[2,3-b]pyridine **10**,

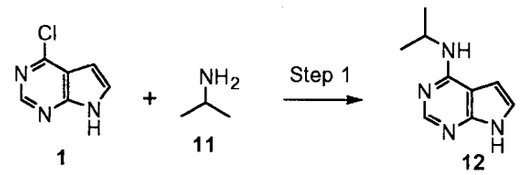


8 , **9** , and **10** ,

are prepared following the protocol of Scheme 1a, replacing methylmagnesium bromide with isopropylmagnesium bromide, isobutylmagnesium bromide, and cyclopropylmagnesium bromide, respectively. MS (ESI) $[M+H^+]^+$ = 162.1 (**8**); and 176.1 (**9**).

[0217] Isopropyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine **12** is synthesized in one step from 4-chloro-7H-pyrrolo[2,3-d]pyrimidine **1** as shown in Scheme 1b.

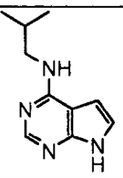
Scheme 1b

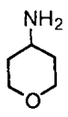
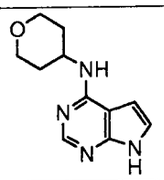
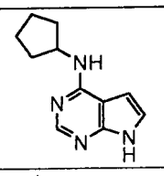
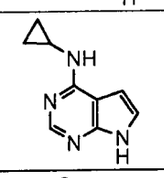
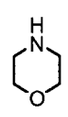
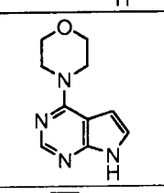
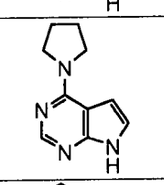
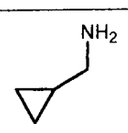
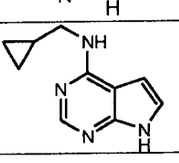


Step 1 – Preparation of isopropyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine (12):

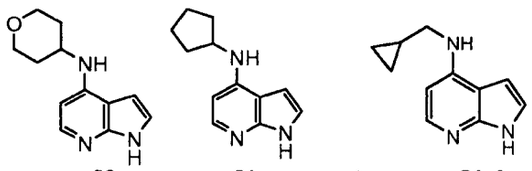
[0218] To 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**1**, 168 mg, 1.09 mmol), 2.00 mL of isopropyl alcohol is added, followed by 2-propanamine (**11**, 0.280 mL, 3.28 mmol). The reaction is heated by microwave at 120 °C for 20 minutes, then an additional 40 minutes. Another 0.250 mL of 2-propanamine is added and heated at 120 °C for 60 minutes. The reaction is poured into water and extracted with ethyl acetate. The organic layer is concentrated under vacuum and purified by silica gel column chromatography, eluting with a gradient of 1-5% methanol in dichloromethane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**12**, 172 mg). MS (ESI) $[M+H^+]^+$ = 176.85.

[0219] Additional compounds are prepared following the protocol of Scheme 1b. In some instances, without limitation, 4-chloro-7H-pyrrolo[2,3-d]pyrimidine **1** is reacted directly in the liquid amine compound without additional solvent (e.g. isopropyl alcohol). Compounds are prepared substituting 2-propanamine **11** with a suitable amine. The following compounds are made using this procedure:
Isobutyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine (**13**),
(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-(tetrahydro-pyran-4-yl)-amine (**14**),
Cyclopentyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine (**15**),
Cyclopropyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine (**16**)
4-Morpholin-4-yl-7H-pyrrolo[2,3-d]pyrimidine (**17**), and
4-Pyrrolidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine (**18**).
The following table indicates the amine compound (column 2) used to afford the desired compound (column 3). The compound number is provided in column 1, and the observed mass is in column 4.

Compound number	Amine	Compound structure	MS (ESI) $[M+H^+]^+$
13			191.1

14			219.1
15			203.0
16			175.1
17			205.0
18			189.0
19			189.0

[0220] 1H-Pyrrolo[2,3-b]pyridine compounds similarly substituted at the 4-position, (1H-pyrrolo[2,3-b]pyridin-4-yl)-(tetrahydro-pyran-4-yl)-amine **20**, cyclopentyl-(1H-pyrrolo[2,3-b]pyridin-4-yl)-amine **21**, and cyclopropylmethyl-(1H-pyrrolo[2,3-b]pyridin-4-yl)-amine **21-A**,

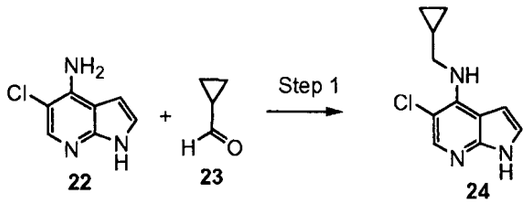


20 , **21** , and **21-A** ,

are also prepared following the protocol of Scheme 1b, substituting 2-propanamine **11** with tetrahydro-pyran-4-ylamine, cyclopentylamine, and c-cyclopropyl-methylamine, respectively, and using 4-chloro-1H-pyrrolo[2,3-b]pyridine in place of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine **1**. These reactions are carried out using toluene as solvent, and include Pd(OR)(OAc) and potassium tert-butoxide in the reaction. Pd(OR)(OAc) is a palladium catalyst wherein R is 2-(di-tert-butylphosphino)biphenyl, prepared by combining palladium(II) acetate (225 mg, 1 mmol) with 2-(di-tert-butylphosphino)biphenyl (299 mg, 1 mmol) in 15 mL of toluene. The solution is shaken overnight at room temperature for use in the above reaction. MS (ESI) $[M+H^+]^+$ = 218.1 (**20**), 202.4 (**21**), and 187.8 (**21-A**).

[0221] (5-Chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)-cyclopropylmethyl-amine **24** is synthesized in one step from 5-chloro-1H-pyrrolo[2,3-b]pyridin-4-ylamine **22** as shown in Scheme 1c.

Scheme 1c



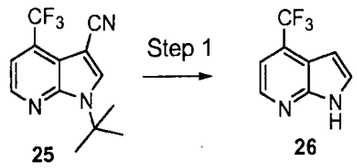
22 **23** **24**

Step 1 – Preparation of (5-chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)-cyclopropylmethyl-amine (24):

[0222] In a round bottom flask, 5-chloro-1H-pyrrolo[2,3-b]pyridin-4-ylamine (**22**, 0.21 g, 1.25 mmol) is combined with 3.5 mL of ethanol, acetic acid (0.38 g, 6.25 mmol), silica bound sodium cyanoborohydride (1.1g, 1.02 mmol), and cyclopropanecarbaldehyde (**23**, 0.26 g, 4 mmol). The reaction mixture was stirred over night at room temperature, heated up to 145°C until the reaction was complete, filtered, concentrated, and purified by flash chromatography to provide compound as a solid (**24** , 0.191g; yield = 69%).

[0223] 4-Trifluoromethyl-1H-pyrrolo[2,3-b]pyridine **26** is synthesized in one step from 1-tert-butyl-4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile **25** as shown in Scheme 1d.

Scheme 1d

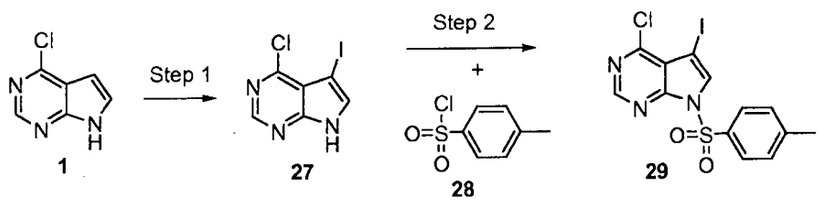


Step 1 – Preparation of 4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine (26):

[0224] 1-tert-Butyl-4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**25**, 1.071 g, 4.007 mmol) is dissolved in 10 mL of aqueous 60% sulfuric acid and stirred at 120 °C for 20 hours. The reaction is adjusted to pH ~7 with sodium hydroxide and aqueous saturated sodium bicarbonate, then extracted with ethyl acetate. The organic layer is washed with water, then brine and dried with magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with ethyl acetate and hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**26**, 373 mg). MS (ESI) $[M+H^+]^+ = 187.1$.

[0225] 4-chloro-5-iodo-7-(toluene-4-sulfonyl)-7H-pyrrolo[2,3-d]pyrimidine **29** is synthesized in two steps from 4-chloro-7H-pyrrolo[2,3-d]pyrimidine **1** as shown in Scheme 1e.

Scheme 1e



Step 1 – Preparation of 4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (27):

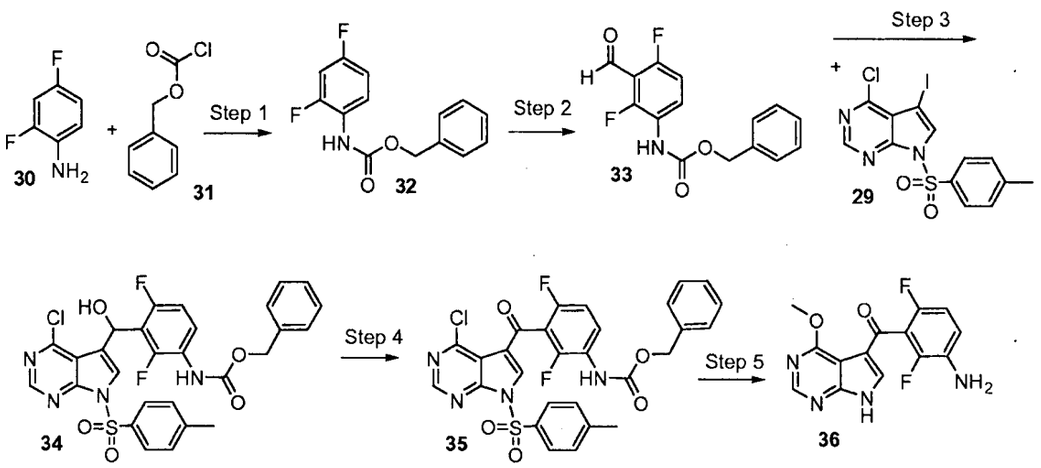
[0226] To 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**1**, 1.21 g, 7.88 mmol) dissolved in 50 mL of dichloromethane, N-iodosuccinimide (1.95 g, 8.67 mmol) is added and the reaction is stirred at room temperature overnight. The reaction is quenched with 50% aqueous sodium thiosulfate and the mixture is filtered through celite. The aqueous layer is extracted with ethyl acetate. The organic layers are combined and washed with water, then brine, and dried with sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with ethyl acetate and dichloromethane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**27**, 1.383 g). MS (ESI) $[M+H^+]^+ = 279.8, 281.8$.

Step 2 – Preparation of 4-chloro-5-iodo-7-(toluene-4-sulfonyl)-7H-pyrrolo[2,3-d]pyrimidine (29):

[0227] To 4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (**27**, 2.45 g, 8.77 mmol) in 68 mL of tetrahydrofuran, sodium hydride (0.4208 g, 10.52 mmol) is added and the reaction is stirred at room temperature for 30 minutes. 4-Methyl-benzenesulfonyl chloride (**28**, 1.838 g, 9.643 mmol) is added and the reaction stirred at room temperature overnight. Water is added and the reaction is extracted with ethyl acetate, resulting in some precipitate that is removed by filtration. The aqueous layer is separated and extracted with ethyl acetate. The organic layers are combined, washed with water, then brine and dried with magnesium sulfate, filtered and the filtrate concentrated under vacuum. The residue is suspended in ethyl acetate, sonicated for 30 minutes, and the solid collected by filtration to provide the desired compound (**29**, 3.325 g). MS (ESI) $[M+H^+]^+ = 433.8$.

[0228] (3-Amino-2,6-difluoro-phenyl)-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone **36** is synthesized in five steps from 2,4-difluoroaniline **30** as shown in Scheme 1f.

Scheme 1f



Step 1 - Preparation of (2,4-difluoro-phenyl)-carbamic acid benzyl ester (32):

[0229] To 2,4-difluoro-phenylamine (**30**, 7.0 mL, 70.0 mmol) in 100 mL of dichloromethane, pyridine (11 mL, 0.14 mol) and benzyl chloroformate (**31**, 11.9 mL, 83.4 mmol) are added. The reaction mixture is stirred at ambient temperature for 1.5 hours. The reaction mixture is concentrated under vacuum and the residue is partitioned between ethyl acetate and potassium bisulfate solution. The organic layer is dried with magnesium sulfate, filtered, and the filtrate concentrated under vacuum. The resulting material is crystallized from hexanes to provide the desired compound (**32**, 15.6 g, 85%).

Step 2 - Preparation of (2,4-difluoro-3-formyl-phenyl)-carbamic acid benzyl ester (33):

[0230] In a round bottom flask (2,4-difluoro-phenyl)-carbamic acid benzyl ester (**30**, 3.83 g, 14.5 mmol) is combined with 148 mL of tetrahydrofuran. The solution is chilled to -78 °C and n-butyllithium (19.1 mL, 1.60 M in hexane, 30.0 mmol) is added over 30 minutes, followed by the addition of N,N-dimethylformamide (1.12 mL, 14.5 mol). The reaction mixture is allowed to warm to ambient temperature and is stirred overnight, then poured into water and extracted with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is crystallized from ether to provide the desired compound (**33**, 3.0 g, 71%).

Step 3 – Preparation of (3-{[4-chloro-7-(toluene-4-sulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-hydroxy-methyl}-2,4-difluoro-phenyl)-carbamic acid benzyl ester (34):

[0231] In a round bottom flask, 4-chloro-5-iodo-7-(toluene-4-sulfonyl)-7H-pyrrolo[2,3-d]pyrimidine (**29**, 1.549 g, 3.572 mmol) is combined with 25.0 mL of tetrahydrofuran and the solution is cooled to -50 °C under nitrogen. Isopropylmagnesium chloride (2.76 mL, 2.0 M in tetrahydrofuran, 5.00 mmol) is added slowly and the reaction is allowed to warm to 5 °C over 70 minutes, then cooled to -45 °C. In a separate vessel, (2,4-difluoro-3-formyl-phenyl)-carbamic acid benzyl ester (**33**, 805 mg, 2.76 mmol) in 5 mL of tetrhydrofuran is cooled to -5 °C and o-tolylmagnesium chloride (2.76 mL, 1 M in tetrahydrofuran, 2.76 mmol) is added dropwise slowly, maintaining the temperature at -5 °C for 1 hour. This is then cooled to -30 °C and added to the above 4-chloro-5-iodo-7-(toluene-4-sulfonyl)-7H-pyrrolo[2,3-d]pyrimidine reaction mixture. The resulting reaction mixture is warmed to room temperature over 2-3 hours, then quenched with the addition of 1 M aqueous citric acid and extracted with ethyl acetate. The organic layer is washed with water, brine and dried over magnesium sulfate, then filtered and the filtrate is concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with ethyl acetate and hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**34**, 445 mg). MS(ESI) $[M+H^+]^+ = 598.8$.

Step 4 – Preparation of {3-[4-chloro-7-(toluene-4-sulfonyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-carbamic acid benzyl ester (35):

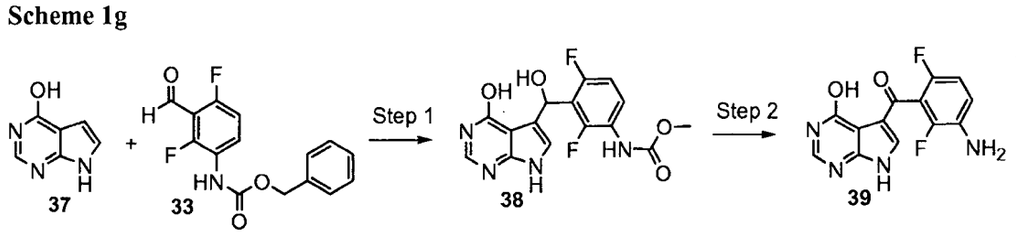
[0232] In a round bottom flask, (3-{[4-chloro-7-(toluene-4-sulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-hydroxy-methyl}-2,4-difluoro-phenyl)-carbamic acid benzyl ester (**34**, 311 mg, 0.519 mmol) is dissolved in 35 mL of tetrahydrofuran and Dess-Martin periodinane (242 mg, 0.571 mmol) is added. The resulting mixture is stirred at room temperature, and additional Dess-Martin periodinane is added. After 60 minutes, the reaction is quenched with water and extracted with ethyl acetate. The organic layer is washed with aqueous sodium bicarbonate, then brine, and dried with magnesium sulfate, filtered and the filtrate is concentrated under vacuum. The resulting material is purified by silica gel chromatography eluting with ethyl acetate and hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**35**, 152 mg). MS(ESI) $[M+H^+]^+ = 596.8$.

Step 5 – Preparation of (3-amino-2,6-difluoro-phenyl)-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (36):

[0233] {3-[4-Chloro-7-(toluene-4-sulfonyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-carbamic acid benzyl ester (**35**, 152 mg, 0.255 mmol) is combined with 15 mL of methanol and potassium hydroxide (1.06 g, 18.9 mmol) is added. The mixture is heated at 70 °C for 36 hours, then 6 N aqueous hydrochloric acid is added and the mixture is extracted with ethyl acetate. The organic layer is washed with brine, then dried with magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with ethyl acetate and hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**36**, 0.03 mg). MS(ESI) $[M+H]^+ = 305.1$.

[0234] (3-Amino-2,6-difluoro-phenyl)-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone **39** is synthesized in two steps from 7H-pyrrolo[2,3-d]pyrimidin-4-ol **37** and (2,4-difluoro-3-formyl-phenyl)-carbamic acid benzyl ester **33** as shown in Scheme 1g.

Scheme 1g



Step 1 – Preparation of {2,4-difluoro-3-[hydroxy-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methyl]-

phenyl}-carbamic acid methyl ester (38):

[0235] In a reaction vessel, 7H-pyrrolo[2,3-d]pyrimidin-4-ol (**37**, 855 mg, 6.33 mmol) is combined with (2,4-difluoro-3-formyl-phenyl)-carbamic acid benzyl ester (**33**, 2.03 g, 6.96 mmol) and potassium hydroxide (1.06 g, 19.0 mmol) and 5 mL of methanol is added. The resulting solution is stirred at 50 °C for 2 days. The reaction is diluted with 1N hydrochloric acid and extracted with ethyl acetate, and the resulting solids collected by filtration and dried under vacuum. The organic layer is separated from the filtrate and the aqueous layer extracted twice more with ethyl acetate. The organic layers are combined and washed with water, brine, dried with magnesium sulfate and filtered. The filtrate is concentrated under vacuum and the resulting material is suspended in acetonitrile and sonicated for 1 hour. The solid is collected by filtration and dried under vacuum, then combined with the first solid collected to provide the desired compound (**38**, 2.05 g). MS(ESI) $[M-H^+]^-$ = 349.0.

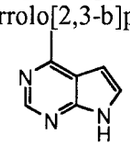
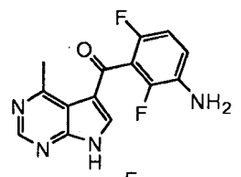
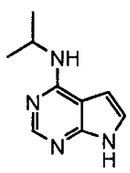
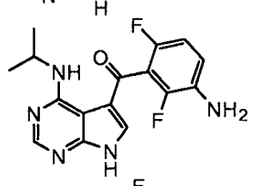
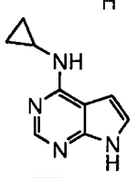
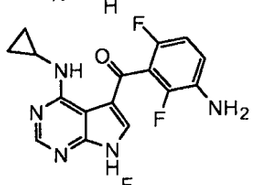
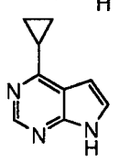
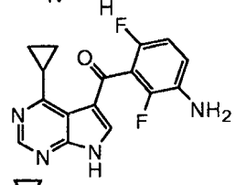
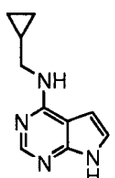
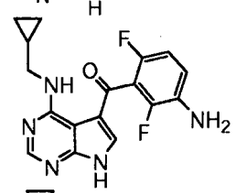
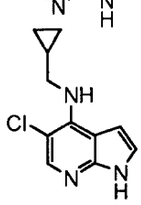
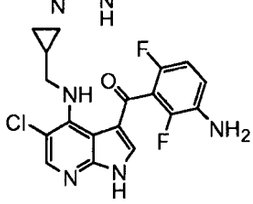
Step 2 – Preparation of (3-amino-2,6-difluoro-phenyl)-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (39):

[0236] In a reaction vessel, {2,4-difluoro-3-[hydroxy-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methyl]-phenyl}-carbamic acid methyl ester (**38**, 690 mg, 1.97 mmol) is dissolved in 200 mL of tetrahydrofuran and Dess-Martin periodinane (877.3 mg, 2.068 mmol) is added. The resulting mixture is stirred at room temperature for 3 hours, then 20 mL of saturated aqueous sodium bicarbonate, 5 mL of saturated aqueous sodium thiosulfate, and 100 mL of ethyl acetate are added for extraction. The organic layer is isolated and the aqueous layer extracted with 50 mL of ethyl acetate. The organic fractions are combined and washed with water, then brine, dried with magnesium sulfate, filtered and the filtrate is concentrated under vacuum. The resulting material is suspended in acetonitrile, sonicated for 1 hour, then filtered to collect the solid material, which is then washed with acetonitrile. The resulting material is suspended in 15 mL of dioxane, and combined with 15 mL of 10N aqueous sodium hydroxide, and heated to reflux for 5 hours. The reaction mixture is adjusted to approximately pH 6 with 6N hydrochloric acid and extracted with ethyl acetate. The organic layer is concentrated under vacuum and the resulting material purified by silica gel chromatography eluting with methanol and dichloromethane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**39**, 287 mg). MS(ESI) $[M-H^+]^-$ = 289.1.

[0237] Additional compounds are prepared following the protocol of Scheme 1f or 1g, reacting a suitable 7H-pyrrolo[2,3-d]pyrimidine or 1H-pyrrolo[2,3-b]pyridine with aldehyde **33** (or alternatively with (2,4-difluoro-3-formyl-phenyl)-carbamic acid methyl ester). The following compounds are made using this procedure:

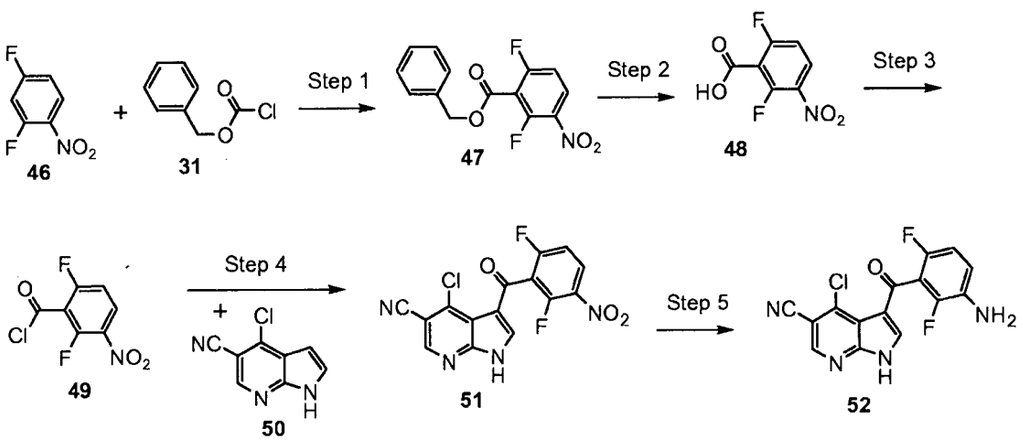
(3-Amino-2,6-difluoro-phenyl)-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**40**),
(3-amino-2,6-difluoro-phenyl)-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**41**),
(3-Amino-2,6-difluoro-phenyl)-(4-cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**42**),
(3-Amino-2,6-difluoro-phenyl)-(4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**43**),
(3-Amino-2,6-difluoro-phenyl)-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-methanone (**44**), and
(3-Amino-2,6-difluoro-phenyl)-[5-chloro-4-(cyclopropylmethyl-amino)-1H-pyrrolo[2,3-b]pyridin-3-yl]-methanone (**45**).

The following table indicates the 7H-pyrrolo[2,3-d]pyrimidine or 1H-pyrrolo[2,3-b]pyridine compound (column 2) used to afford the desired compound (column 3). The compound number is provided in column 1, and the observed mass is in column 4.

Compound number	7H-pyrrolo[2,3-d]pyrimidine or 1H-pyrrolo[2,3-b]pyridine	Compound structure	MS (ESI) $[M+H^+]^+$
40			
41			331.9
42			329.9
43			314.9
44			343.9
45			

[0238] 3-(3-Amino-2,6-difluoro-benzoyl)-4-chloro-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **52** is synthesized in five steps from 2,4-difluoro-1-nitro-benzene **46** and benzyl chloroformate **31** as shown in Scheme 1h.

Scheme 1h



Step 1 – Preparation of 2,6-difluoro-3-nitro-benzoic acid benzyl ester (47):

[0239] 2,4-Difluoro-1-nitro-benzene (**46**, 1.4 mL, 13.0 mmol) and benzyl chloroformate (**31**, 10.42 g, 61.1 mmol) in 20 mL of tetrahydrofuran is cooled to -78 °C and stirred for 1 hour. Lithium diisopropylamine (1.5 g, 14.0 mmol) is added dropwise and the reaction is stirred at -78 °C for 1 hour, then warmed to room temperature over 2 hours. The reaction was purified by silica gel chromatography, eluting with hexane:ethyl acetate 90:10. Appropriate fractions are combined and concentrated under vacuum, then washed with methanol and the solid collected by filtration to provide the desired compound (**47**, 110 mg).

Step 2 – Preparation of 2,6-difluoro-3-nitro-benzoic acid (48):

[0240] To 2,6-difluoro-3-nitro-benzoic acid benzyl ester (**47**, 750 mg, 2.6 mmol) in 4 mL of tetrahydrofuran and 2 mL of water, sodium hydroxide (0.2 g, 5.0 mmol) is added and the reaction is stirred for 2 hours. The reaction is acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic layer is concentrated under vacuum to provide the desired compound (**48**, 300 mg).

Step 3 – Preparation of 2,6-difluoro-3-nitro-benzoyl chloride (49):

[0241] To 2,6-difluoro-3-nitro-benzoic acid (**48**, 5.50 g, 27.1 mmol), thionyl chloride (20 mL, 300 mmol) is added, followed by N,N-dimethylformamide (0.1 mL, 2.0 mmol) and the reaction is heated in an

oil bath at 80 °C. After overnight reaction, the reaction mixture is concentrated under vacuum, azeotroped with toluene (2X) to provide the desired compound (**49**, 5.95 g).

Step 4 – Preparation of 4-chloro-3-(2,6-difluoro-3-nitro-benzoyl)-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (51):

[0242] In a vial, 4-chloro-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**50**, 500 mg, 2.82 mmol) is cooled in an ice water bath, and trifluoromethanesulfonic acid (2.49 mL, 28.15 mmol) is added. The solution is stirred at 0-5 °C for 5 minutes, then 2,6-difluoro-3-nitro-benzoyl chloride (**49**, 748.5 mg, 3.38 mmol) is added. The reaction is stirred at 0-5 °C for 1 hour, then warmed to room temperature and stirred for 4 days. The reaction is quenched with 5 mL of methanol, and stirred at room temperature for 1 hour. The reaction is poured into saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer is washed with water, brine, dried with magnesium sulfate, filtered and the filtrate is concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 0-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**51**, 134 mg).

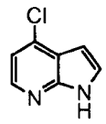
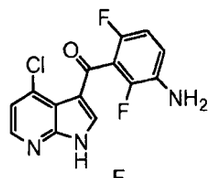
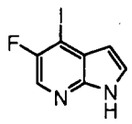
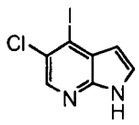
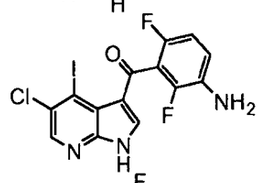
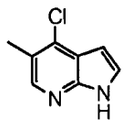
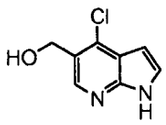
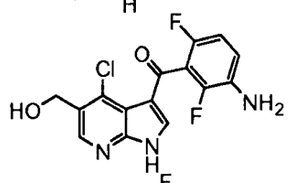
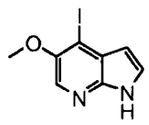
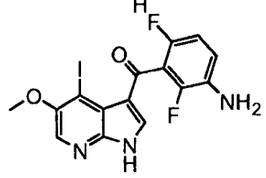
Step 5 – Preparation of 3-(3-amino-2,6-difluoro-benzoyl)-4-chloro-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (52):

[0243] In a round bottom flask, 4-chloro-3-(2,6-difluoro-3-nitro-benzoyl)-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**51**, 0.15 g, 0.42 mmol) in 10 mL of ethanol and 10 mL of tetrhydrofuran, tin(II) chloride (0.1 mL, 2.1 mmol) is added. An additional 10 mL of tetrahydrofuran is added to give a clear solution, and the reaction is heated at 60 °C for 24 hours. The reaction is combined with 10 mL of water and 10 mL of saturated aqueous sodium bicarbonate and 20 mL of ethyl acetate is added. Celite is added with mixing, and then filtered. Brine is added to the filtrate and the layers are separated. The organic layer is washed with water, brine, dried with magenesium sulfate, filtered and the filtrate is concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 0-80% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**52**, 123 mg). MS (ESI) $[M+H^+]^+$ = 332.8 and 334.8.

[0244] Additional substituted (3-amino-2,6-difluoro-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone compounds are prepared following the protocol of Scheme 1h. Compounds are prepared substituting 4-chloro-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **50** with a suitable substituted 1H-pyrrolo[2,3-b]pyridine in step 4. The following compounds are made using this procedure: (3-Amino-2,6-difluoro-phenyl)-(4-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**53**),

(3-Amino-2,6-difluoro-phenyl)-(5-fluoro-4-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**54**),
(3-Amino-2,6-difluoro-phenyl)-(5-chloro-4-iodo-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**55**),
(3-Amino-2,6-difluoro-phenyl)-(4-chloro-5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**56**),
(3-Amino-2,6-difluoro-phenyl)-(4-chloro-5-hydroxymethyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**57**), and
(3-Amino-2,6-difluoro-phenyl)-(4-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**58**).

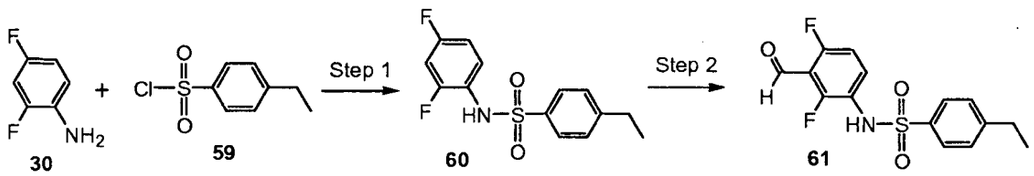
The following table indicates the 1H-pyrrolo[2,3-b]pyridine compound (column 2) used in step 4 to afford the desired compound (column 3). The compound number is provided in column 1, and the observed mass is in column 4.

Compound number	1H-pyrrolo[2,3-b]pyridine	Compound structure	MS (ESI) $[M-H^+]^-$
53			308.3
54			418.0
55			
56			
57			
58			

Example 2: Synthesis of N-(2,4-difluoro-3-formyl-phenyl)-4-ethyl-benzenesulfonamide 61.

[0245] N-(2,4-Difluoro-3-formyl-phenyl)-4-ethyl-benzenesulfonamide **61** is synthesized in two steps from 2,4-difluoro-phenylamine **30** and 4-ethyl-benzenesulfonyl chloride **59** as shown in Scheme 2.

Scheme 2



Step 1– Preparation of N-(2,4-difluoro-phenyl)-4-ethyl-benzenesulfonamide (60):

[0246] To 2,4-difluoro-phenylamine (**30**, 2.0 g, 15.5 mmol) in 20 mL of dichloromethane, pyridine (1.326 mL, 16.4 mmol) and dimethylaminopyridine (0.076 g, 0.62 mmol) are added followed by the dropwise addition of 4-ethyl-benzenesulfonyl chloride (**59**, 3.357 g, 16.4 mmol) and the reaction is heated to reflux overnight. The reaction is concentrated under vacuum to dryness, then brought up in ethyl acetate and water for extraction. The organic layer is isolated and concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with a gradient of 10-20% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**60**, 4.344 g).

Step 2– Preparation of N-(2,4-difluoro-3-formyl-phenyl)-4-ethyl-benzenesulfonamide (61):

[0247] To N,N-diisopropylamine (4.50 mL, 32.1 mmol) in 130 mL of tetrahydrofuran, n-butyllithium (12.8 mL, 2.50 M in hexane, 32.1 mmol) is added at -78 °C under nitrogen. After 15 minutes, N-(2,4-difluoro-phenyl)-4-ethyl-benzenesulfonamide (**60**, 4.344 g, 14.61 mmol) in 20 mL of tetrahydrofuran is added at -78 °C under nitrogen. After 30 minutes, N,N-dimethylformamide (2.83 mL, 36.5 mmol) is added and the reaction continued at -78 °C under nitrogen for 1 hour, then warmed to room temperature over 60 minutes. The reaction is quenched with 6 mL of 6 N aqueous hydrochloric acid. The aqueous layer is extracted with ethyl acetate. The organic layers are combined and washed with brine, dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with a gradient of 5-35% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**61**, 2.634 g). MS (ESI) $[M-H^+]^-$ = 324.2.

[0248] Additional aldehyde compounds are prepared following the protocol of Scheme 2. Compounds are prepared substituting 4-ethyl-benzenesulfonyl chloride **59** with a suitable sulfonyl chloride in step 1. The following compounds are made using this procedure:

2-Methyl-propane-1-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide (**62**),

N-(2,4-Difluoro-3-formyl-phenyl)-4-trifluoromethyl-benzenesulfonamide (**63**),

N-(2,4-Difluoro-3-formyl-phenyl)-4-propyl-benzenesulfonamide (**64**),

N-(2,4-Difluoro-3-formyl-phenyl)-4-isopropyl-benzenesulfonamide (**65**),

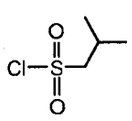
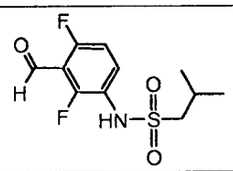
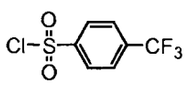
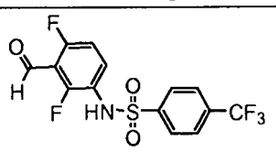
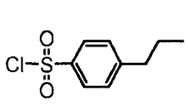
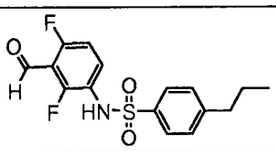
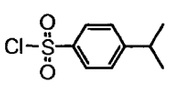
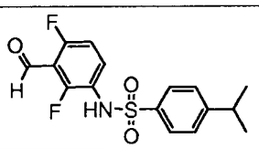
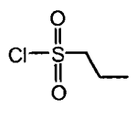
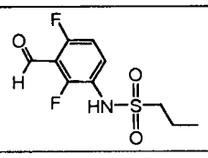
Propane-1-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide (**66**),

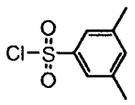
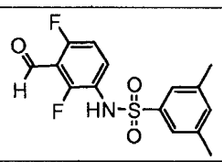
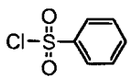
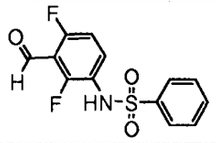
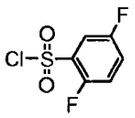
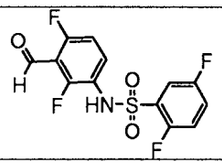
N-(2,4-Difluoro-3-formyl-phenyl)-3,5-dimethyl-benzenesulfonamide (**67**),

N-(2,4-Difluoro-3-formyl-phenyl)-benzenesulfonamide (**68**), and

N-(2,4-Difluoro-3-formyl-phenyl)-2,5-difluoro-benzenesulfonamide (**69**).

The following table indicates the sulfonyl chloride compound (column 2) used in step 1 to afford the desired aldehyde compound (column 3). The compound number is provided in column 1, and the observed mass is in column 4.

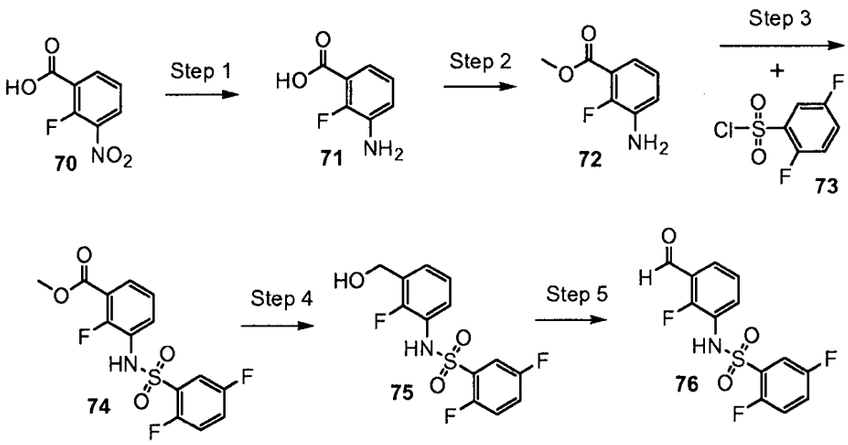
Compound number	Sulfonyl chloride	Aldehyde structure	MS (ESI) $[M-H^+]^-$
62			276.1
63			364.1
64			338.18
65			338.2
66			262

67			323.9
68			
69			331.9

Example 3: Synthesis of 2,5-difluoro-N-(2-fluoro-3-formyl-phenyl)-benzenesulfonamide 76.

[0249] 2,5-Difluoro-N-(2-fluoro-3-formyl-phenyl)-benzenesulfonamide **76** is prepared in five steps from 2-fluoro-3-nitro-benzoic acid **70** as shown in Scheme 3.

Scheme 3



Step 1– Preparation of 3-amino-2-fluoro-benzoic acid (71):

[0250] To 2-fluoro-3-nitro-benzoic acid (**70**, 6.77 g, 36.6 mmol) in 150 mL of methanol, Palladium on carbon (5:95 Palladium:Carbon, 0.338 g, 0.159 mmol) is added under a balloon of hydrogen. The reaction is stirred at room temperature for 40 hours, then a new balloon of hydrogen is attached, and the reaction continued for 5 hours. The reaction is filtered and the filtrate is concentrated under vacuum to provide the desired compound (**71**, 5.62 g). MS (ESI) $[M-H^+]^-$ = 154.1.

Step 2– Preparation of 3-amino-2-fluoro-benzoic acid methyl ester (72):

[0251] In a round bottom flask, 3-amino-2-fluoro-benzoic acid (**71**, 2.51 g, 16.2 mmol) is dissolved in 100 mL of methanol and 1 mL of concentrated sulfuric acid is added. The reaction is heated to reflux for 24 hours and an additional 1 mL of concentrated sulfuric acid is added. The reaction is heated to reflux another 20 hours, then extracted with ethyl acetate and saturated aqueous sodium chloride. The organic layer is isolated and washed with water, sodium bicarbonate, and brine, then dried with magnesium sulfate, and filtered. The filtrate is concentrated under vacuum to provide the desired compound (**72**, 2.688 g).

Step 3– Preparation of 3-(2,5-difluoro-benzenesulfonylamino)-2-fluoro-benzoic acid methyl ester (74):

[0252] To 3-amino-2-fluoro-benzoic acid methyl ester (**72**, 1.08 g, 6.4 mmol) in 40.64 mL of dichloromethane, pyridine (1.29 mL, 16 mmol) is added, followed by 2,5-difluorobenzenesulfonyl chloride (**73**, 3.391 g, 16 mmol). The reaction is stirred at room temperature overnight, then quenched with 1M aqueous hydrochloric acid. The organic layer is removed and the aqueous layer is extracted with dichloromethane. The organic layers are combined and washed with brine, then dried over sodium sulfate, filtered and the filtrate is concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with ethyl acetate and hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**74**, 0.956 g). MS (ESI) $[M\text{-}H^+]^-$ = 344.

Step 4– Preparation of 2,5-difluoro-N-(2-fluoro-3-hydroxymethyl-phenyl)-benzenesulfonamide (75):

[0253] To 3-(2,5-difluoro-benzenesulfonylamino)-2-fluoro-benzoic acid methyl ester (**74**, 0.955 g, 2.8 mmol) in 22 mL of tetrahydrofuran, lithium tetrahydroaluminate (6 mL, 1M in tetrahydrofuran, 6 mmol) is added at -40 °C under nitrogen. The reaction is allowed to warm to room temperature and stirred overnight. The reaction is poured into 1M aqueous sodium hydroxide, then neutralized with 1M aqueous hydrochloric acid. The solids are filtered through a bed of celite, and the celite bed is washed with ethyl acetate and tetrahydrofuran. The filtrate layers are separated and the aqueous layer is extracted with ethyl acetate. The organic layers are combined and washed with brine, dried over sodium sulfate, filtered and the filtrate is concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with ethyl acetate and dichloromethane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**75**, 0.875 g). MS (ESI) $[M\text{-}H^+]^-$ = 316.

Step 5– Preparation of 2,5-difluoro-N-(2-fluoro-3-formyl-phenyl)-benzenesulfonamide (76):

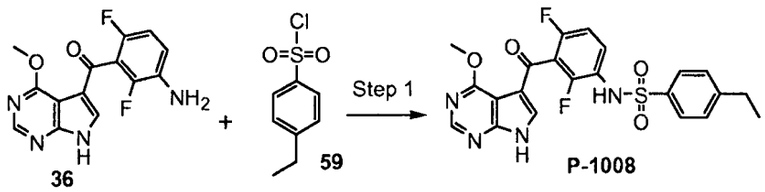
[0254] 2,5-Difluoro-N-(2-fluoro-3-hydroxymethyl-phenyl)-benzenesulfonamide (**75**, 950 mg, 2.99 mmol) and stabilized 2-iodoxybenzoic acid (2.608 g, 45%, 4.2 mmol) are dissolved in 150 mL of

tetrahydrofuran and the reaction is stirred at room temperature for 16 hours. The reaction is poured into water and extracted with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, filtered and the filtrate is concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with ethyl acetate and dichloromethane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**76**, 0.944 g). MS (ESI) $[M-H^+]^-$ = 314.

Example 4: Synthesis of N-[2,4-difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide P-1008.

[0255] N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide **P-1008** is prepared in one step from (3-amino-2,6-difluoro-phenyl)-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone **36** and 4-ethyl-benzenesulfonyl chloride **59** as shown in Scheme 4.

Scheme 4



*Step 1– Preparation of N-[2,4-difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide (**P-1008**):*

[0256] To (3-amino-2,6-difluoro-phenyl)-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**36**, 30.0 mg, 0.0986 mmol) 1.0 mL of tetrahydrofuran and pyridine (23.9 µL, 0.296 mmol) are added, followed by 4-ethyl-benzenesulfonyl chloride (**59**, 40.4 mg, 0.197 mmol). The reaction vial is stirred at room temperature for 5 days, then extracted by adding aqueous saturated sodium chloride and ethyl acetate. The organic layer is washed with water, then sodium bicarbonate, then brine, and dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with ethyl acetate and hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**P-1008**, 27 mg). MS (ESI) $[M+H^+]^+$ = 473.0.

[0257] Additional compounds are prepared following the protocol of Scheme 4, optionally replacing (3-amino-2,6-difluoro-phenyl)-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone **36** with an

appropriately 4-substituted (3-amino-2,6-difluoro-phenyl)-(7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone or suitably substituted (3-amino-2,6-difluoro-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone and optionally replacing 4-ethyl-benzenesulfonyl chloride **59** with an appropriate sulfonyl chloride. The following compounds are made using this procedure:

N-[3-(4-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**77**),

6-Methoxy-pyridine-3-sulfonic acid [2,4-difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1018**),

N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-fluoro-4-methoxy-benzenesulfonamide (**P-1036**),

N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1070**),

N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1073**),

N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1104**),

N-[3-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1107**),

4-Cyano-N-[2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-benzenesulfonamide (**P-1108**),

2,2,2-Trifluoro-ethanesulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1109**),

N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-difluoromethoxy-benzenesulfonamide (**P-1110**),

N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1111**),

N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,6-difluoro-benzenesulfonamide (**P-1112**),

N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,4-difluoro-benzenesulfonamide (**P-1113**),

Propane-2-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1114**),

N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-fluoro-

benzenesulfonamide (**P-1115**),
3-Cyano-N-[2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-benzenesulfonamide (**P-1116**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-fluoro-4-methoxy-benzenesulfonamide (**P-1117**),
3,3,3-Trifluoro-propane-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1118**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-difluoromethoxy-benzenesulfonamide (**P-1119**),
1-Ethyl-1H-pyrazole-4-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1120**),
1-Methyl-1H-pyrazole-4-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1121**),
Piperidine-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1122**),
Cyclohexanesulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1123**),
Cyclopentanesulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1124**),
Pyrrolidine-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1125**),
2-Methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1126**),
Diethylamine-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1127**),
Cyclobutanesulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1128**),
Morpholine-4-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1129**),
6-Methoxy-pyridine-3-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1130**),
6-Methyl-pyridine-2-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1131**),

Pyridine-3-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1132**),
Pyridine-2-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1133**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-benzenesulfonamide (**P-1155**),
Dimethylamine-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1156**),
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1183**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,4-difluoro-benzenesulfonamide (**P-1186**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-benzenesulfonamide (**P-1187**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-4-methoxy-benzenesulfonamide (**P-1188**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-fluoro-benzenesulfonamide (**P-1189**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-4-methyl-benzenesulfonamide (**P-1190**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3,5-difluoro-benzenesulfonamide (**P-1191**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-fluoro-2-methyl-benzenesulfonamide (**P-1192**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-5-methyl-benzenesulfonamide (**P-1193**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-5-trifluoromethyl-benzenesulfonamide (**P-1194**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-4-methyl-benzenesulfonamide (**P-1195**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-4-methoxy-benzenesulfonamide (**P-1196**),
5-Chloro-N-{3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-

phenyl}-2-fluoro-benzenesulfonamide (**P-1197**),
3-Chloro-N-{3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1198**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3,4-difluoro-benzenesulfonamide (**P-1199**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-5-trifluoromethyl-benzenesulfonamide (**P-1200**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-2-methyl-benzenesulfonamide (**P-1201**),
4-Chloro-N-{3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-fluoro-benzenesulfonamide (**P-1202**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-5-fluoro-2-methyl-benzenesulfonamide (**P-1203**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-5-fluoro-2-methoxy-benzenesulfonamide (**P-1204**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-3-trifluoromethyl-benzenesulfonamide (**P-1205**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,6-difluoro-benzenesulfonamide (**P-1206**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-benzenesulfonamide (**P-1207**),
Pyridine-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1208**),
4-Methyl-pyridine-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1209**),
6-Fluoro-pyridine-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1210**),
Pyridine-3-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1211**),
4-Chloro-pyridine-3-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1212**),
2-Chloro-pyridine-3-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1213**),

1-Methyl-1H-pyrazole-4-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1214**),
N,N-Dimethylamino-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1215**),
N,N-Diethylamino-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1216**),
Pyrrolidine-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1217**),
Morpholine-4-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1218**),
Tetrahydro-pyran-4-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1219**),
Ethanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1220**),
Propane-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1221**),
Butane-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1222**),
2-Methyl-propane-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1223**),
Butane-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1224**),
Pentane-2-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1225**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-C,C,C-trifluoro-methanesulfonamide (**P-1226**),
2,2,2-Trifluoro-ethanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1227**),
3,3,3-Trifluoro-propane-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1228**),
Cyclohexanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1229**),
Cyclopentanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-

2,4-difluoro-phenyl}-amide (**P-1230**),

Cyclobutanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1231**),

Cyclopropanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1232**),

4,4-Difluoro-cyclohexanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1233**),

3,3-Difluoro-cyclopentanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1234**),

3-Fluoro-cyclopentanesulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1235**),

N-{3-[5-Chloro-4-(cyclopropylmethyl-amino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-2021**),

N-[2,4-Difluoro-3-(5-fluoro-4-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-2025**),

N-[3-(4-Chloro-5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-2026**)

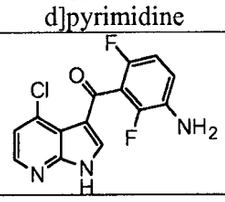
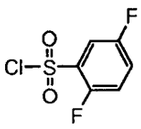
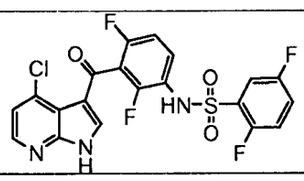
N-[3-(5-Chloro-4-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-2027**),

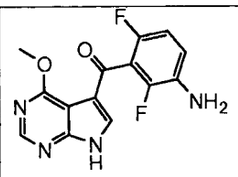
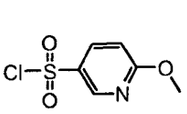
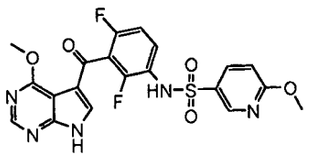
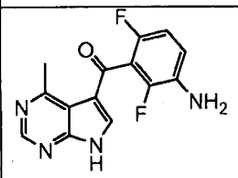
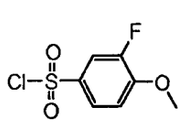
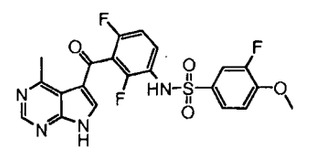
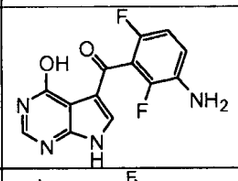
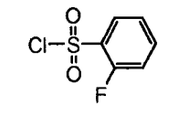
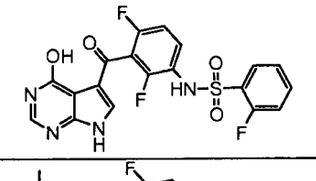
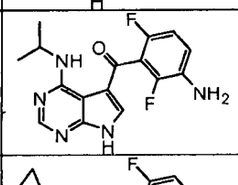
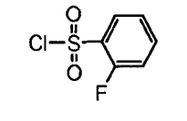
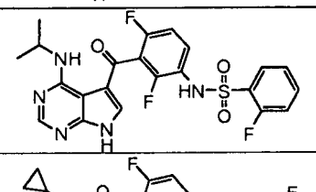
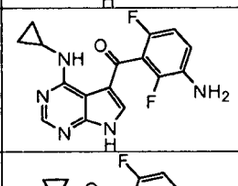
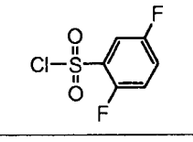
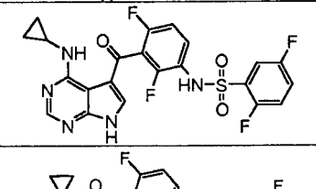
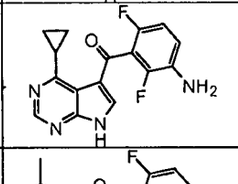
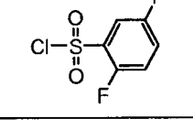
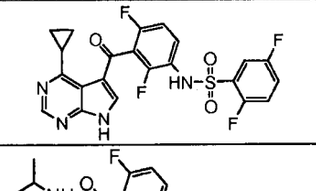
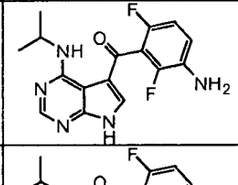
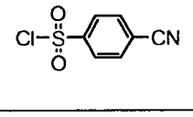
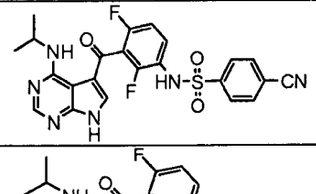
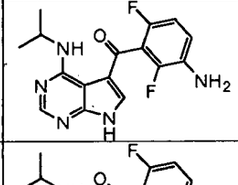
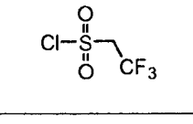
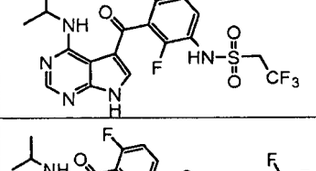
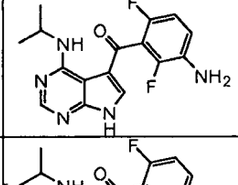
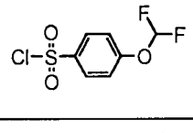
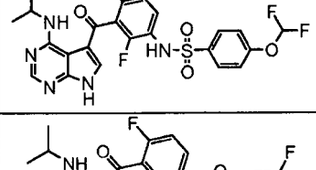
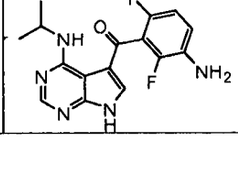
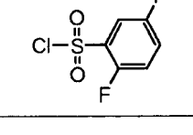
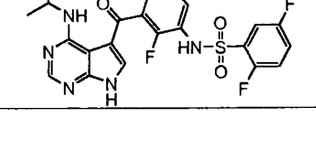
N-[3-(4-Chloro-5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-2028**),

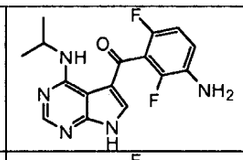
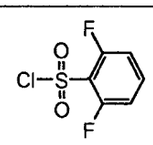
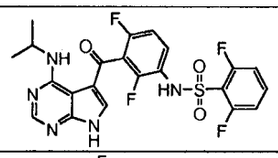
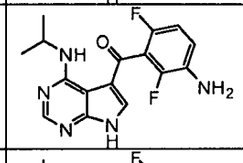
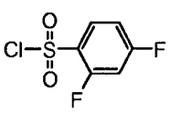
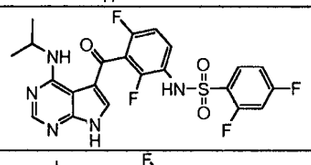
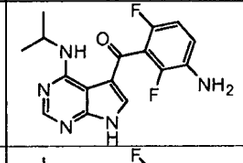
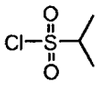
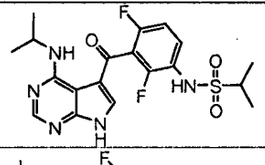
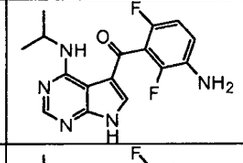
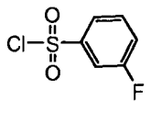
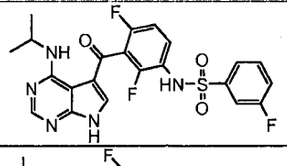
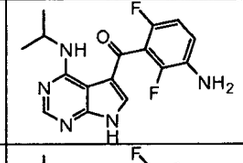
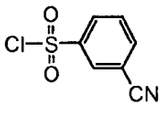
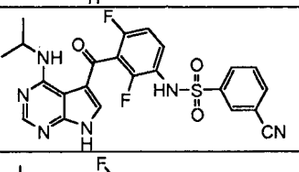
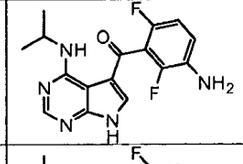
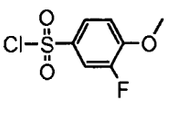
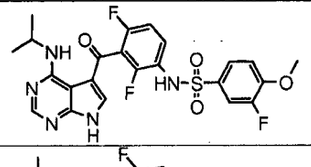
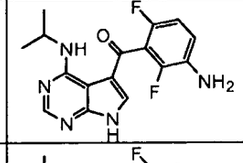
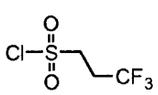
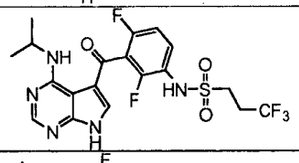
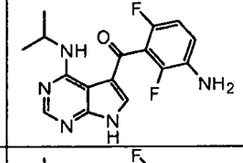
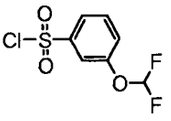
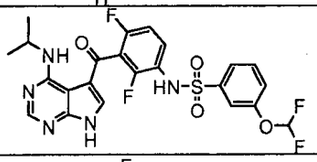
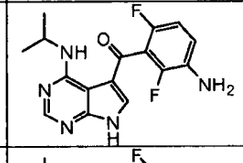
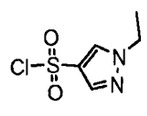
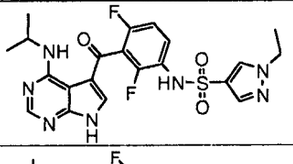
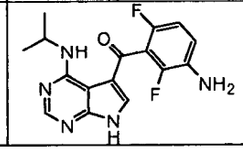
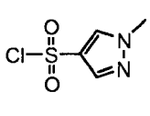
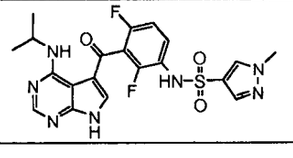
N-[3-(4-Chloro-5-hydroxymethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-2029**), and

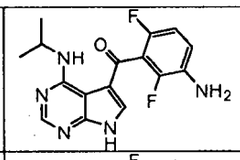
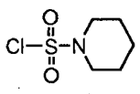
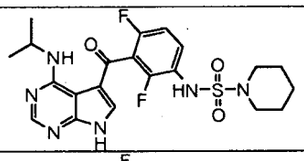
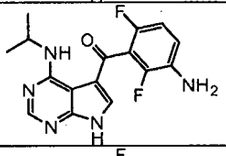
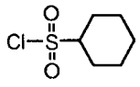
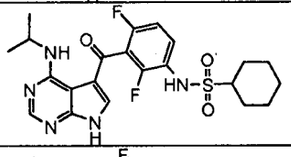
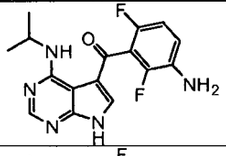
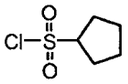
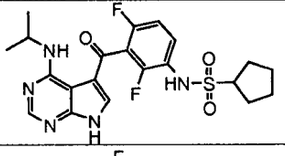
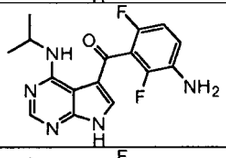
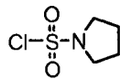
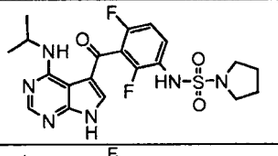
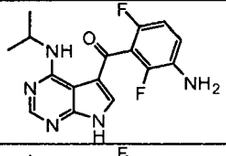
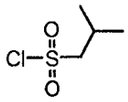
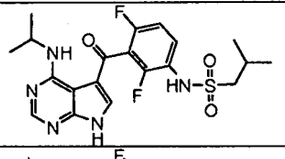
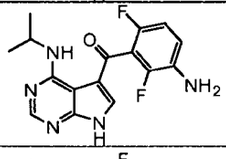
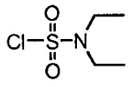
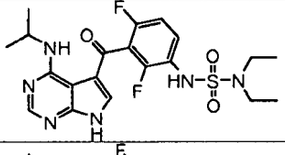
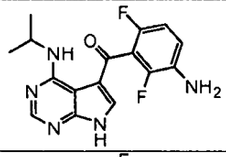
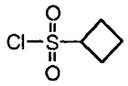
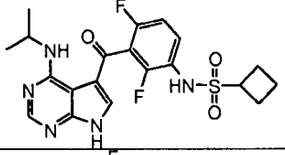
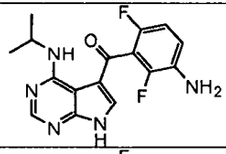
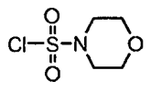
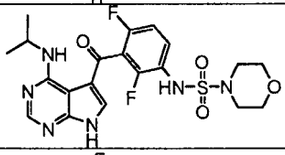
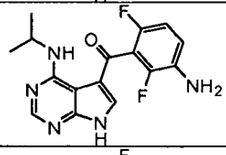
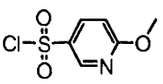
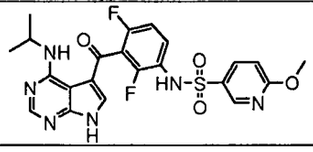
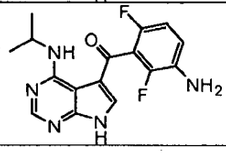
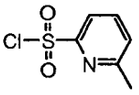
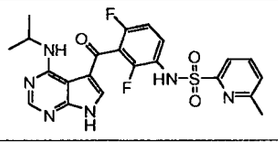
N-[2,4-Difluoro-3-(4-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-2030**).

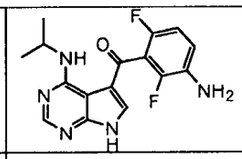
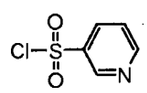
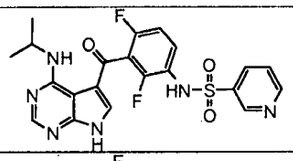
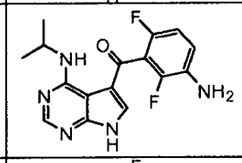
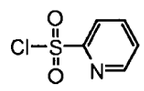
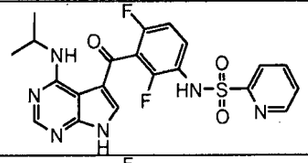
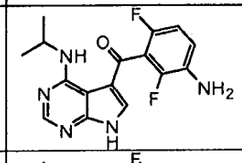
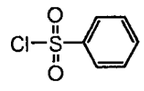
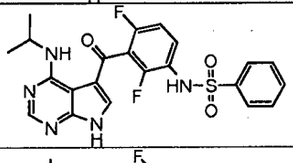
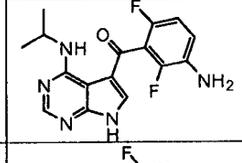
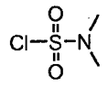
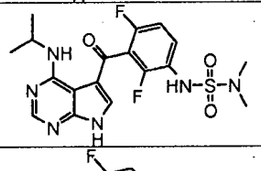
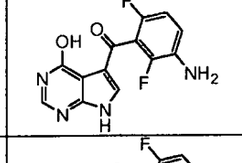
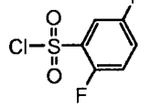
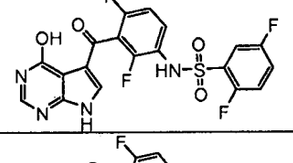
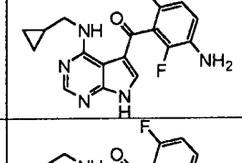
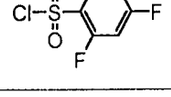
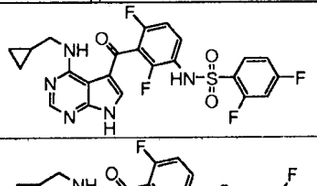
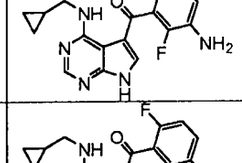
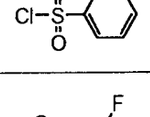
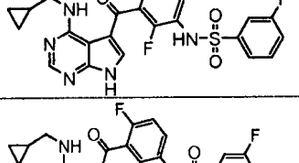
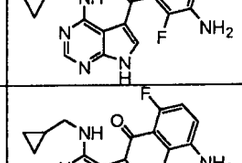
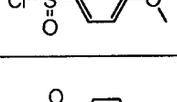
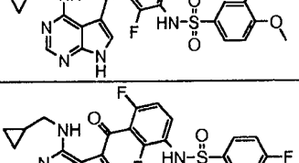
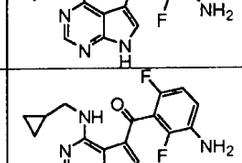
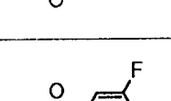
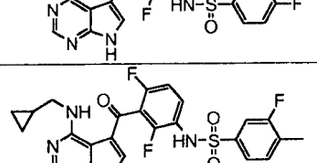
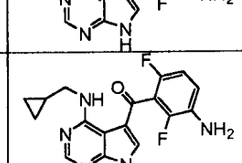
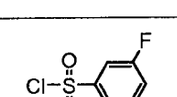
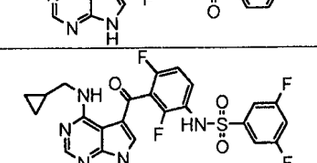
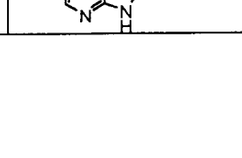
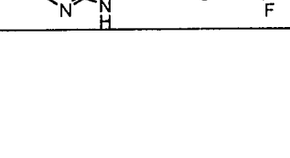
The following table indicates the 7H-pyrrolo[2,3-d]pyrimidine or 1H-pyrrolo[2,3-b]pyridine (column 2) and sulfonyl chloride compound (column 3) used to afford the desired compound (column 4). The compound number is provided in column 1, and the observed mass is in column 5.

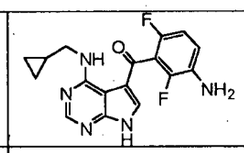
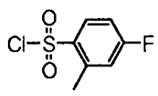
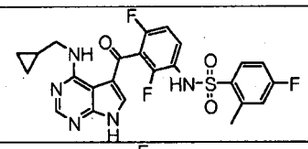
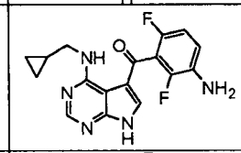
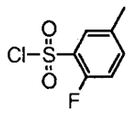
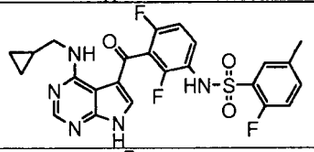
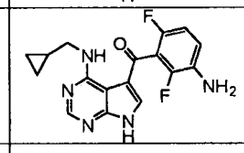
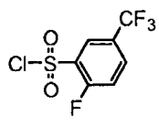
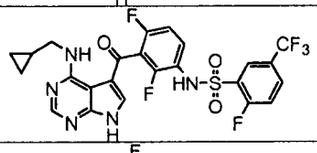
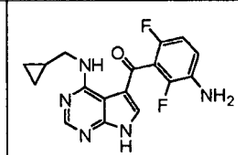
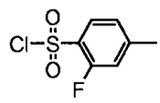
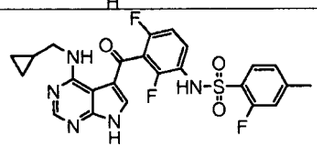
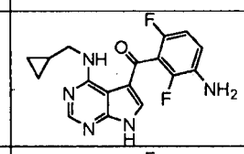
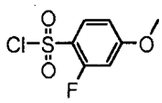
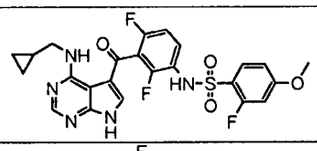
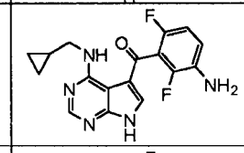
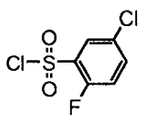
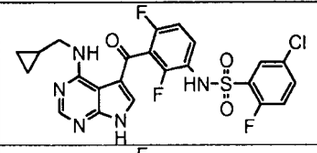
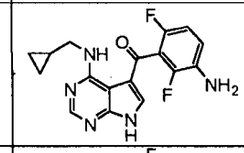
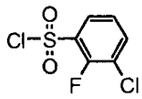
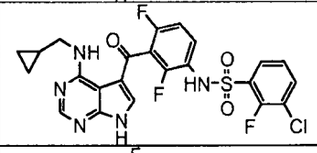
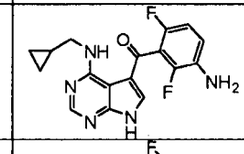
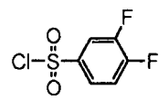
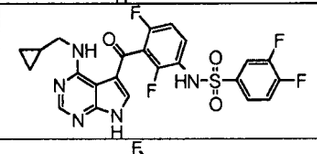
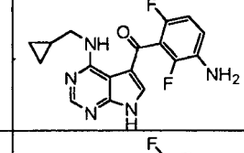
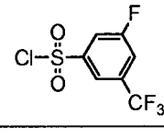
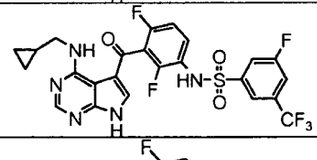
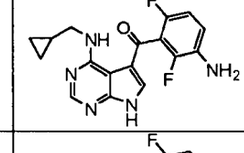
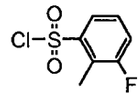
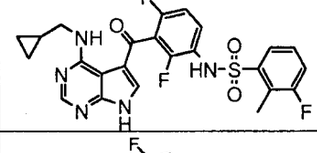
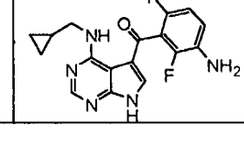
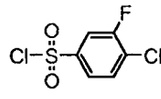
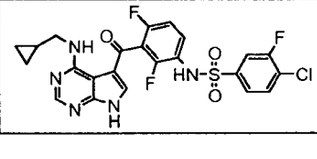
Comp. number	7H-pyrrolo[2,3-d]pyrimidine	Sulfonyl chloride	Compound structure	MS (ESI) $[M+H^+]^+$
77				

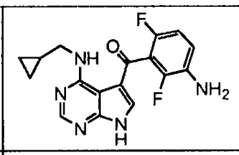
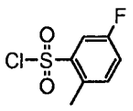
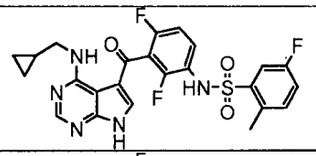
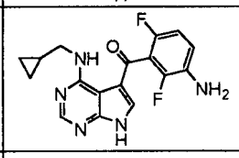
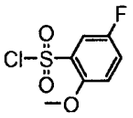
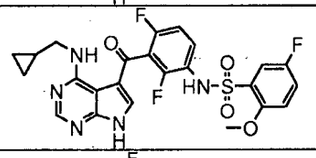
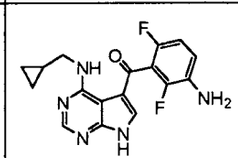
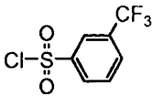
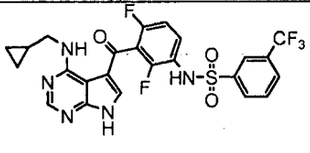
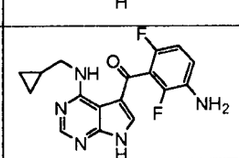
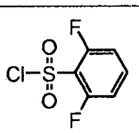
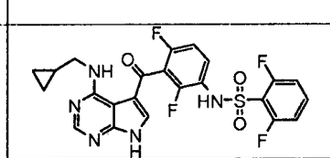
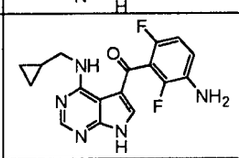
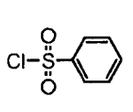
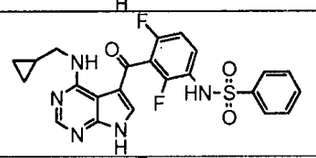
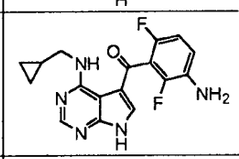
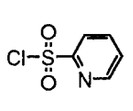
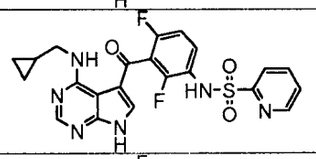
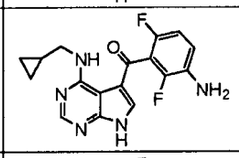
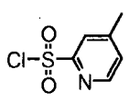
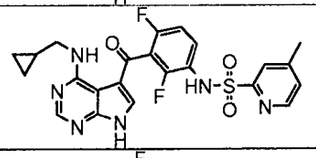
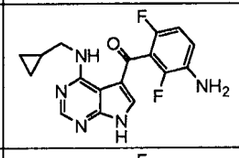
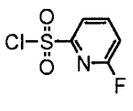
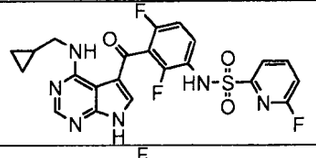
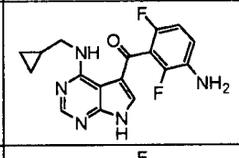
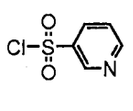
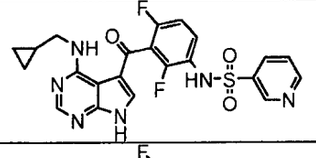
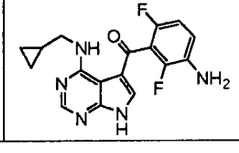
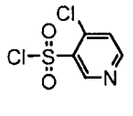
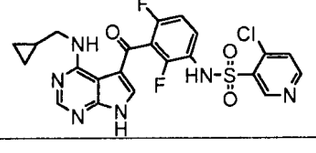
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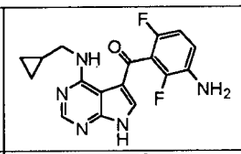
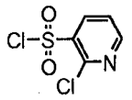
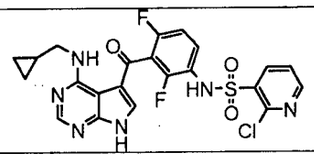
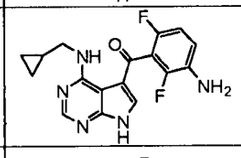
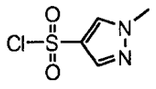
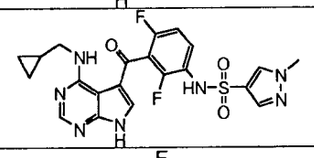
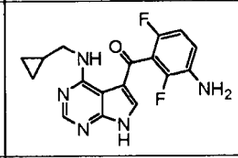
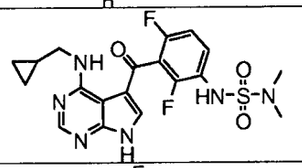
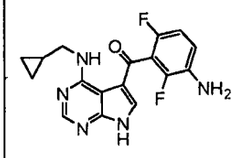
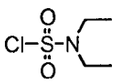
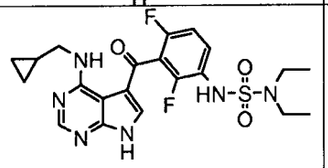
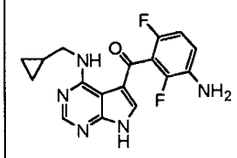
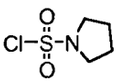
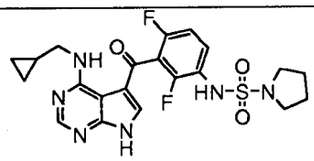
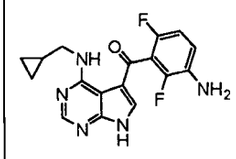
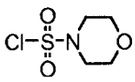
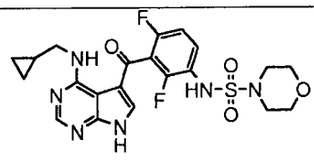
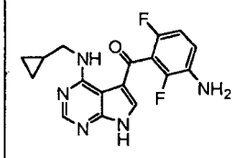
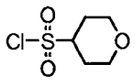
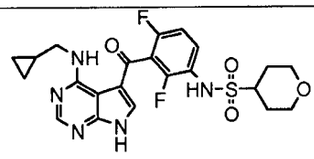
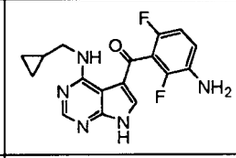
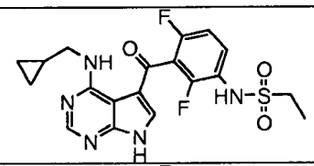
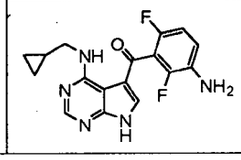
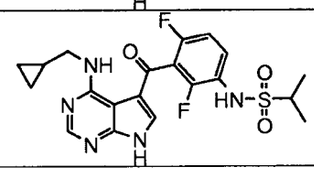
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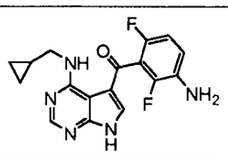
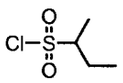
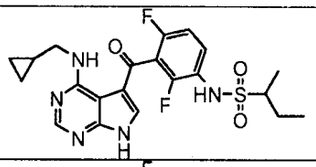
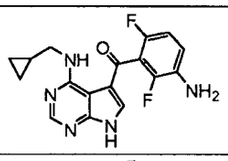
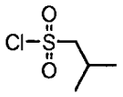
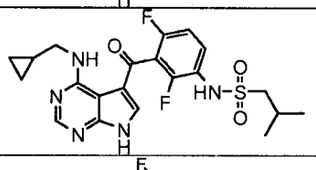
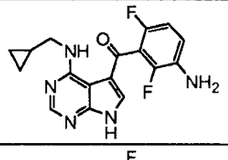
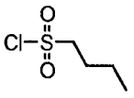
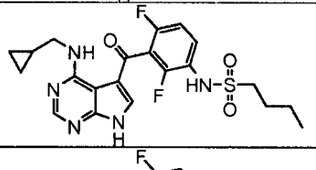
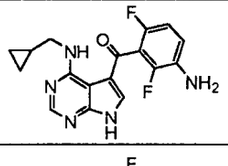
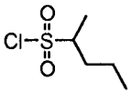
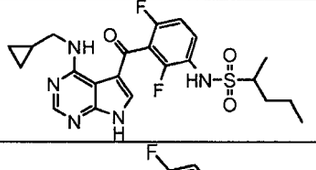
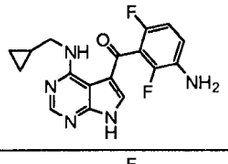
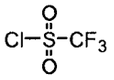
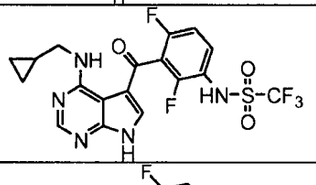
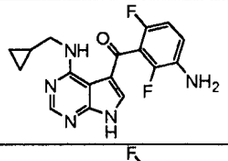
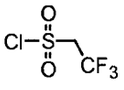
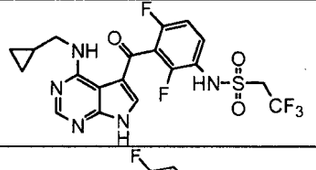
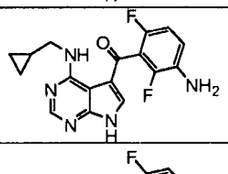
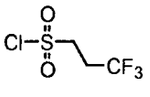
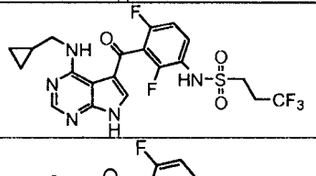
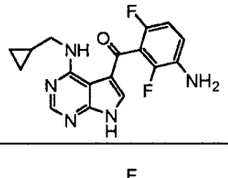
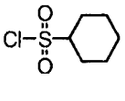
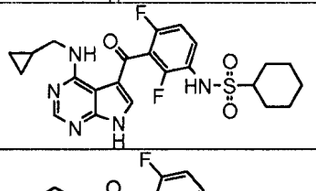
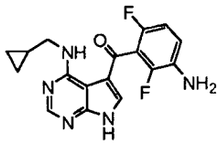
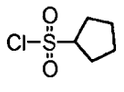
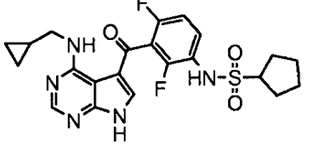
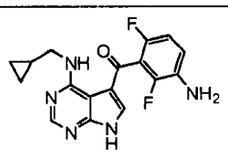
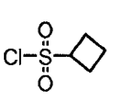
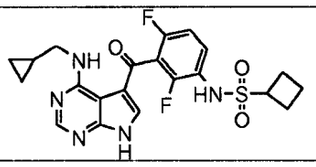
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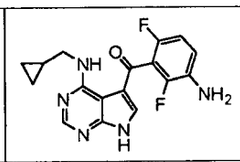
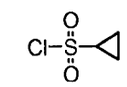
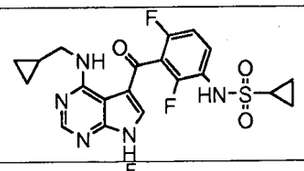
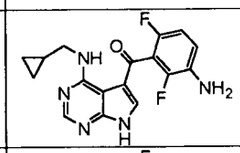
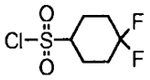
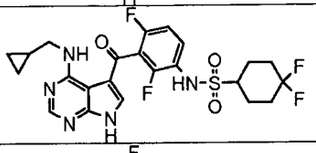
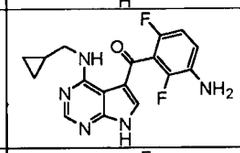
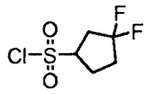
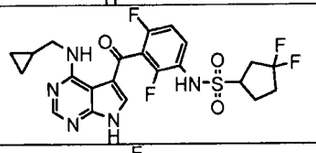
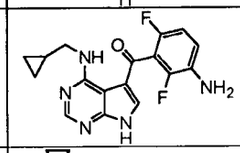
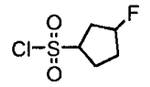
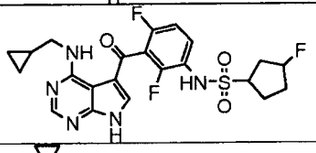
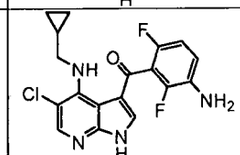
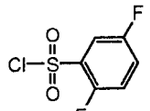
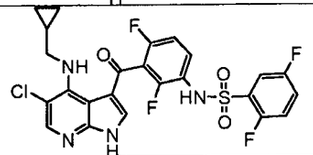
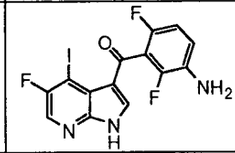
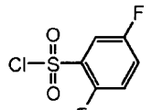
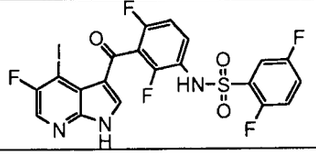
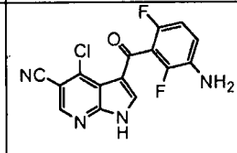
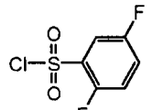
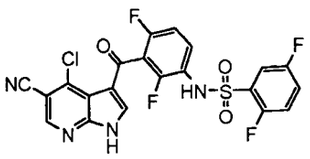
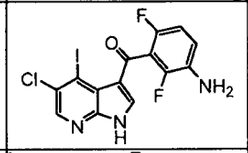
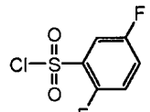
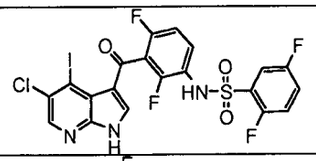
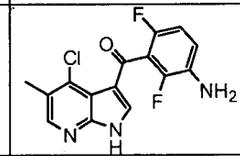
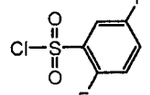
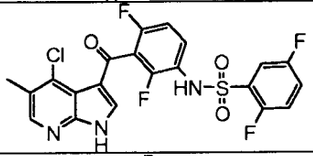
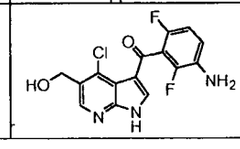
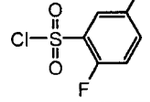
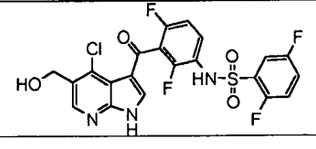
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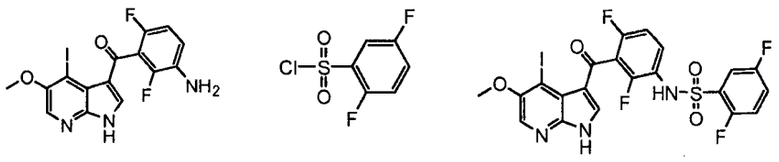
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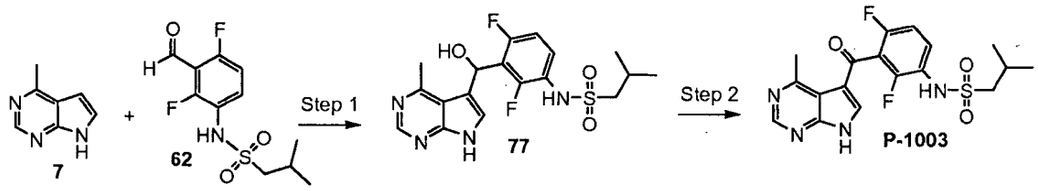
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Example 5: Synthesis of 2-methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide P-1003.

[0258] 2-Methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide **P-1003** is prepared in two steps from 4-methyl-7H-pyrrolo[2,3-d]pyrimidine **7** and 2-methyl-propane-1-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide **62** as shown in Scheme 5.

Scheme 5



Step 1 - Preparation of 2-methyl-propane-1-sulfonic acid {2,4-difluoro-3-[hydroxy-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methyl]-phenyl}-amide (77):

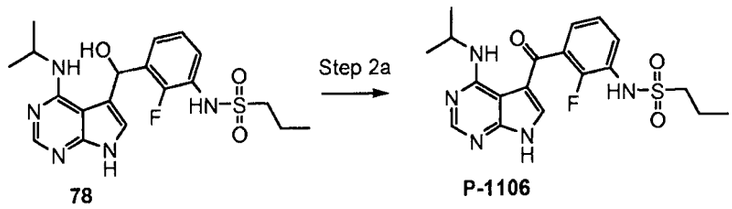
[0259] In a round bottom flask, 4-methyl-7H-pyrrolo[2,3-d]pyrimidine (**7**, 97.0 mg, 0.728 mmol) is combined with 2-methyl-propane-1-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide (**62**, 202 mg, 0.728 mmol), potassium hydroxide (204 mg, 3.64 mmol) and 1.4 mL of methanol. The reaction is stirred at room temperature for 7 hours. The reaction is neutralized with 0.1 N aqueous hydrochloric acid and extracted 3x with ethyl acetate. The combined organic layer is washed with brine, dried with sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with ethyl acetate and dichloromethane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**77**, 113 mg). MS (ESI) $[M-H^+]^-$ = 409.2.

*Step 2 - Preparation of 2-methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1003**):*

[0260] To 2-methyl-propane-1-sulfonic acid {2,4-difluoro-3-[hydroxy-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methyl]-phenyl}-amide (**77**, 99 mg, 0.24 mmol) in 2 mL of tetrahydrofuran, Dess-

Martin periodinane (112 mg, 0.265 mmol) is added and the reaction is stirred at room temperature for 2 hours. The reaction is poured into saturated aqueous sodium thiosulfate along with some sodium bicarbonate solid and extracted with ethyl acetate. The organic layer is washed with water, then brine, and dried with sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with ethyl acetate and dichloromethane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**P-1003**, 28 mg). MS (ESI) $[M+H^+]^+ = 409.3$.

[0261] Propane-1-sulfonic acid [2-fluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide **P-1106** is prepared similarly, reacting isopropyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine **11** and propane-1-sulfonic acid (2-fluoro-3-formyl-phenyl)-amide in Step 1, and further reacting via the following Step 2a:



78 **P-1106**

*Step 2a - Preparation of propane-1-sulfonic acid [2-fluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1106**):*

[0262] To propane-1-sulfonic acid {2-fluoro-3-[hydroxy-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methyl]-phenyl}-amide (**78**, 102 mg, 0.242 mmol) in 1 mL of dimethylsulfoxide, stabilized 2-iodoxybenzoic acid (181 mg, 45%, 0.29 mmol) is added and the reaction is stirred at room temperature for 1 hour. The reaction is poured into water and stirred for 30 minutes, and the precipitate is collected by filtration. The resulting solid is dissolved in 2 mL of tetrahydrofuran and purified by silica gel column chromatography, eluting with ethyl acetate and dichloromethane. Appropriate fractions are combined and concentrated under vacuum to give the desired compound (**P-1106**, 34 mg). MS (ESI) $[M+H^+]^+ = 420.0$.

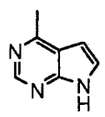
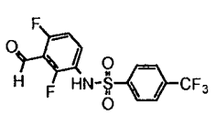
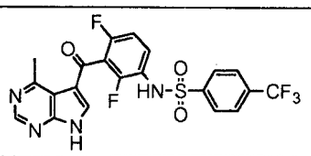
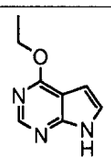
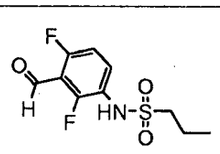
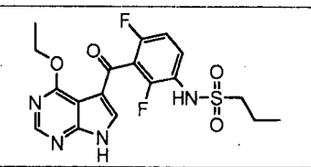
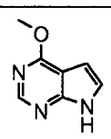
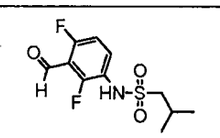
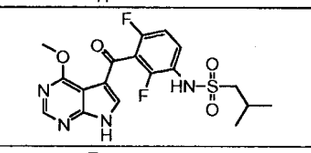
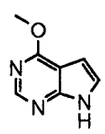
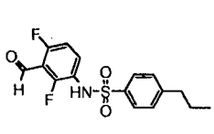
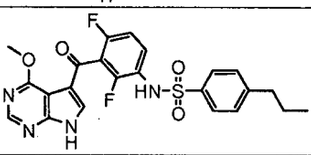
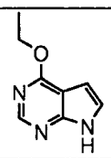
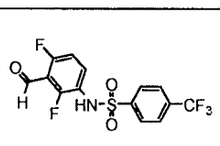
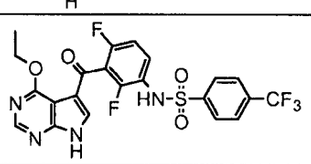
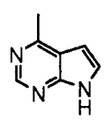
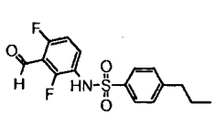
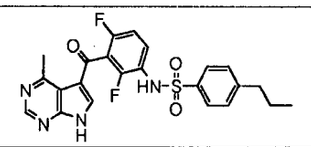
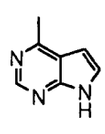
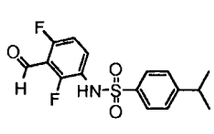
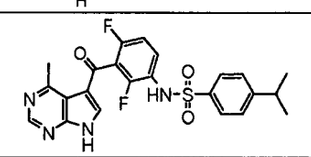
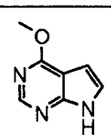
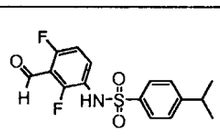
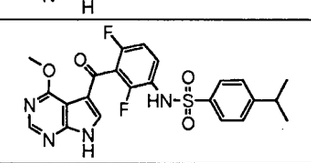
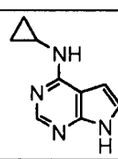
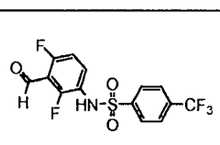
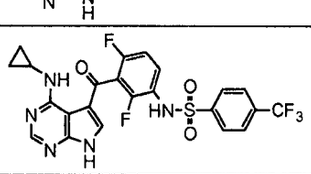
[0263] Additional compounds are prepared following the protocol of Scheme 5. Compounds are prepared optionally substituting 4-methyl-7H-pyrrolo[2,3-d]pyrimidine **7**, with a suitable 7H-pyrrolo[2,3-d]pyrimidine and optionally substituting 2-methyl-propane-1-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide **62** with a suitable aldehyde in step 1. The following compounds are made using this procedure:

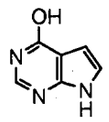
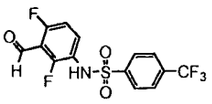
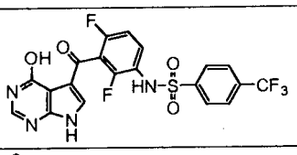
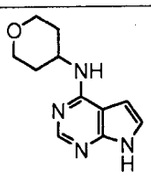
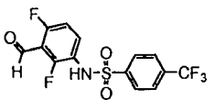
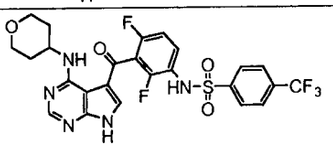
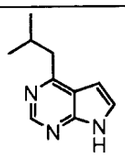
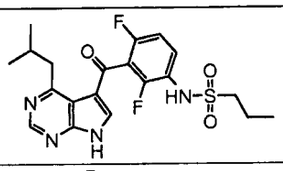
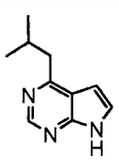
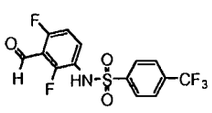
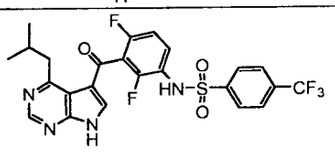
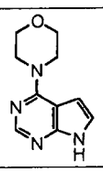
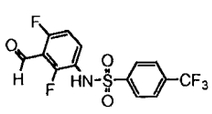
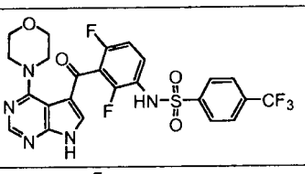
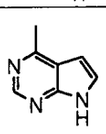
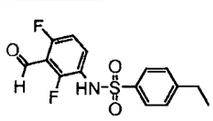
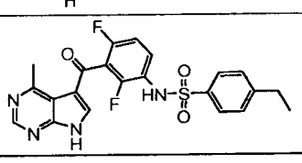
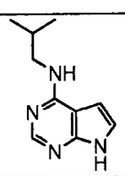
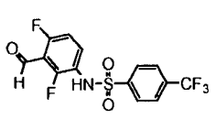
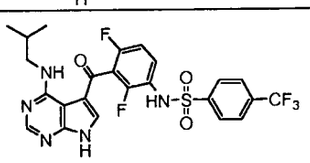
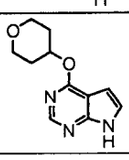
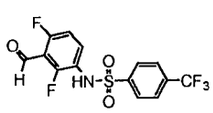
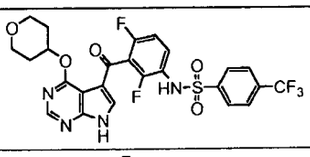
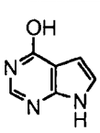
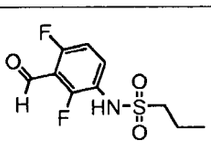
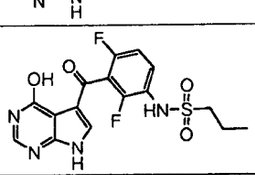
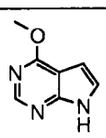
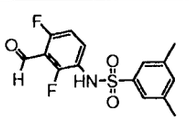
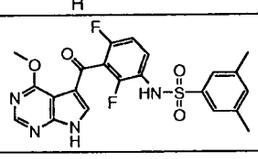
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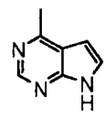
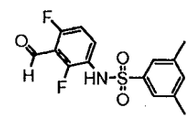
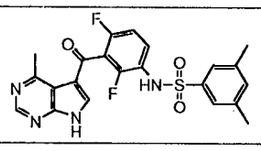
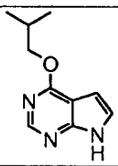
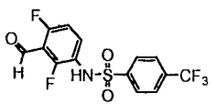
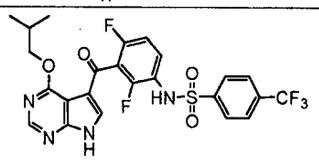
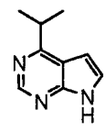
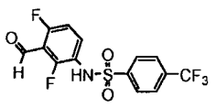
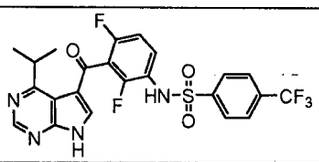
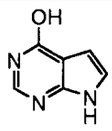
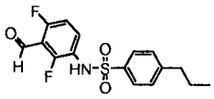
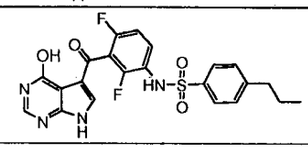
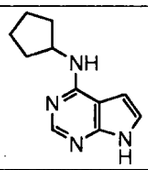
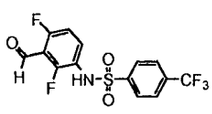
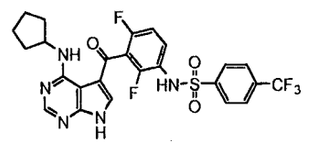
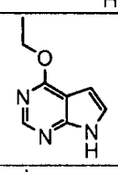
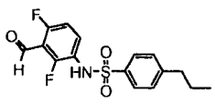
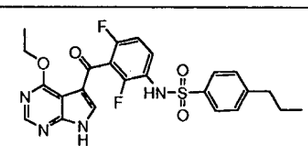
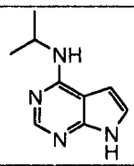
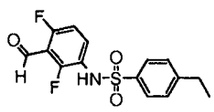
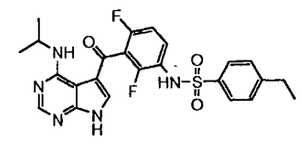
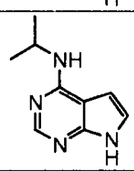
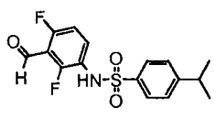
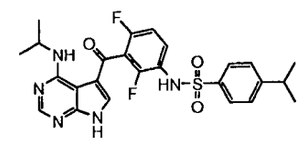
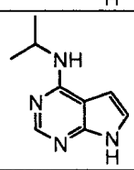
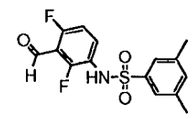
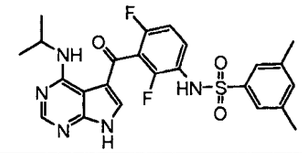
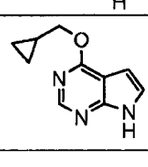
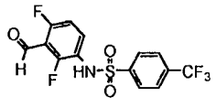
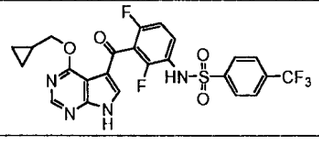
benzenesulfonamide (**P-1001**),
Propane-1-sulfonic acid [3-(4-ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1002**),
2-Methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1004**),
N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1005**),
N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1006**),
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1007**),
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1009**),
N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1010**),
N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1011**),
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1012**),
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1013**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1014**),
N-[2,4-Difluoro-3-(4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1015**),
N-[2,4-Difluoro-3-(4-morpholin-4-yl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1017**),
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide (**P-1019**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1020**),
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1021**),

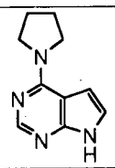
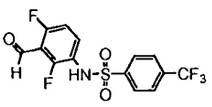
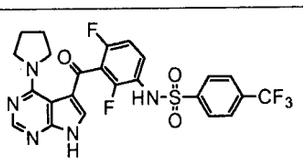
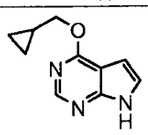
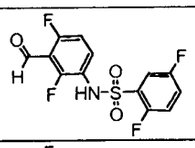
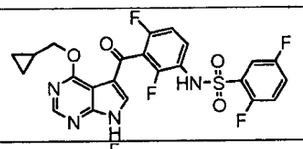
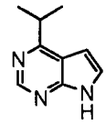
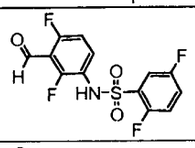
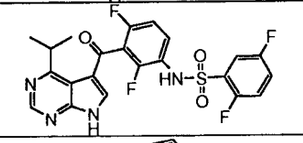
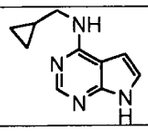
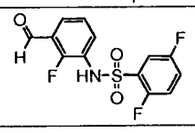
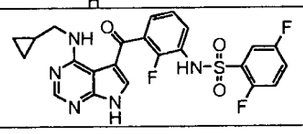
Propane-1-sulfonic acid [2,4-difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1022**),
N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3,5-dimethyl-benzenesulfonamide (**P-1025**),
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3,5-dimethyl-benzenesulfonamide (**P-1027**),
N-[2,4-Difluoro-3-(4-isobutoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1028**),
N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1029**),
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1030**),
N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1035**),
N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1038**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1042**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1044**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3,5-dimethyl-benzenesulfonamide (**P-1045**),
N-[3-(4-Cyclopropylmethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1053**),
N-[2,4-Difluoro-3-(4-pyrrolidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1061**)
N-[3-(4-Cyclopropylmethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1181**),
N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1182**), and
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2-fluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1185**).
The following table indicates the 7H-pyrrolo[2,3-d]pyrimidine (column 2) and aldehyde compound

(column 3) used in step 1 to afford the desired compound (column 4). The compound number is provided in column 1, and the observed mass is in column 5.

Comp. number	7H-pyrrolo[2,3-d]pyrimidine	Aldehyde structure	Compound structure	MS (ESI) $[M+H^+]^+$
P-1001				496.9
P-1002				424.9
P-1004				425.1
P-1005				486.95
P-1006				526.95
P-1007				470.95
P-1009				471.3
P-1010				486.8
P-1011				537.8

P-1012				499.0
P-1013				581.8
P-1014				436.7
P-1015				538.6
P-1017				567.8
P-1019				457.2
P-1020				554.4
P-1021				581.2 $[M-H^+]^-$
P-1022				397.0
P-1025				473.0

P-1027				456.95
P-1028				553.2 $[M-H^+]^-$
P-1029				525.2
P-1030				472.9
P-1035				566.3
P-1038				501.0
P-1042				500.27
P-1044				514.0
P-1045				500.05
P-1053				553.2

P-1061				553.2
P-1181				521.0
P-1182				493.0
P-1185				502.0

[0264] Additional compounds with a 1H-pyrrolo[2,3-b]pyridine core are prepared similarly following the protocol of Scheme 5. Compounds are prepared optionally substituting 4-methyl-7H-pyrrolo[2,3-d]pyrimidine **7**, with a suitable 1H-pyrrolo[2,3-b]pyridine and optionally substituting 2-methyl-propane-1-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide **62** with a suitable aldehyde in step 1. The following compounds are made using this procedure:

Propane-1-sulfonic acid [3-(4-chloro-5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2001**),

Propane-1-sulfonic acid [3-(4-chloro-5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2002**),

Propane-1-sulfonic acid [3-(4-cyano-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2003**),

Propane-1-sulfonic acid [3-(4-chloro-5-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2004**),

Propane-1-sulfonic acid [3-(5-cyano-4-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2005**),

Propane-1-sulfonic acid [3-(5-chloro-4-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2006**),

Propane-1-sulfonic acid [3-(5-chloro-4-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2007**),

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

phenyl]-amide (**P-2008**),

N-[3-(4-Cyano-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2009**),

N-[3-(5-Chloro-4-cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2010**),

N-[3-(5-Chloro-4-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2011**),

Propane-1-sulfonic acid [3-(4-cyclopentylamino-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-2012**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (**P-2013**),

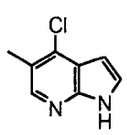
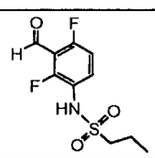
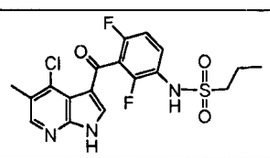
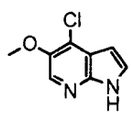
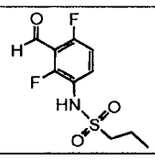
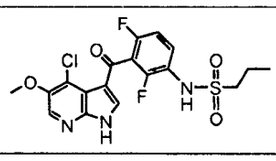
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-2014**),

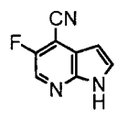
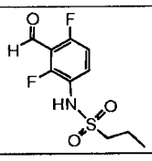
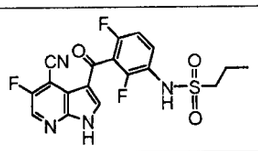
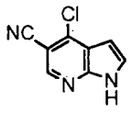
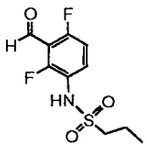
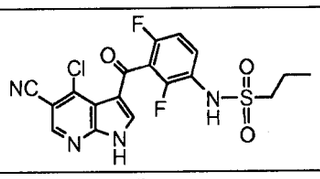
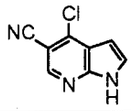
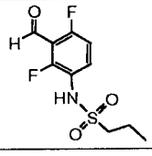
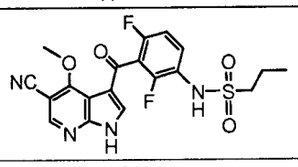
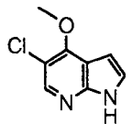
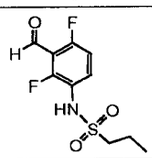
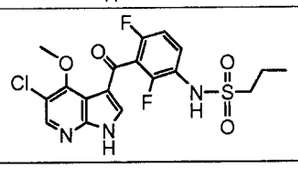
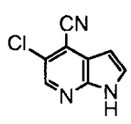
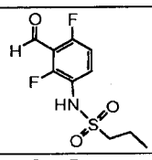
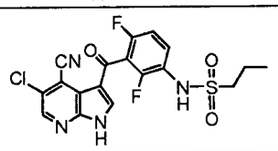
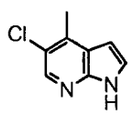
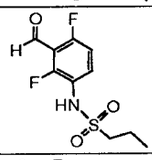
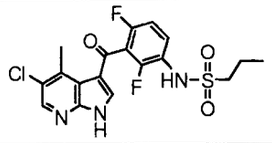
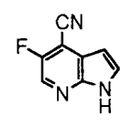
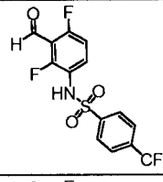
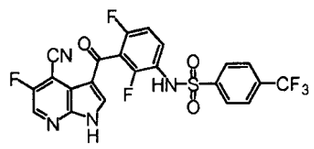
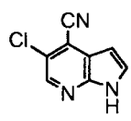
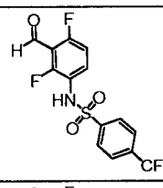
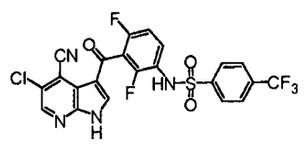
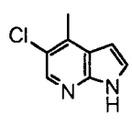
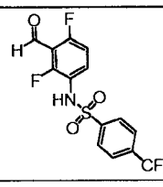
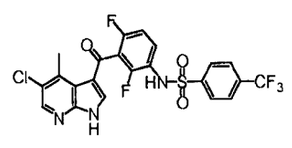
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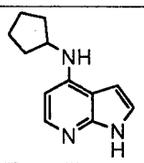
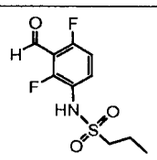
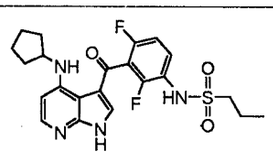
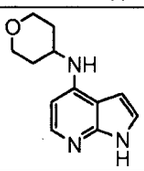
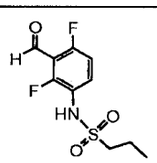
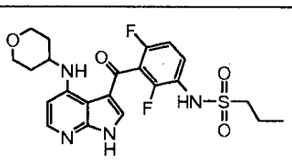
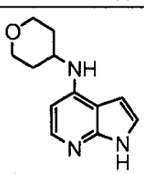
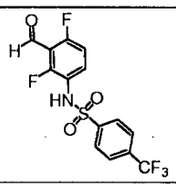
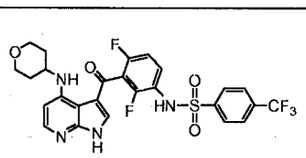
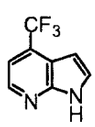
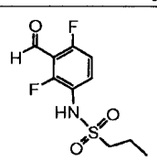
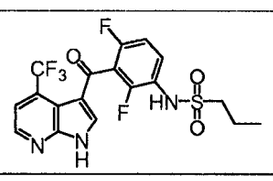
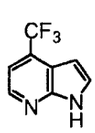
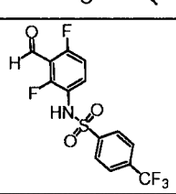
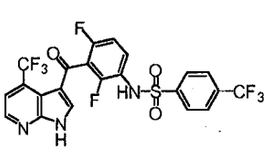
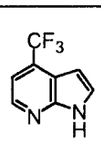
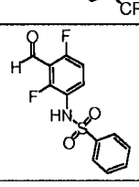
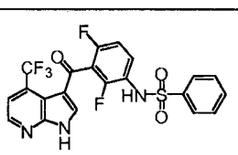
N-[2,4-Difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2016**), and

N-[2,4-Difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide (**P-2017**).

The following table indicates the 1H-pyrrolo[2,3-b]pyridine (column 2) and aldehyde compound (column 3) used in step 1 to afford the desired compound (column 4). The compound number is provided in column 1, and the observed mass is in column 5.

Comp. number	1H-pyrrolo[2,3-b]pyridine	Aldehyde structure	Compound structure	MS (ESI) $[M+H^+]^+$
P-2001				427.9 429.9
P-2002				443.9 446.1

P-2003				421.4 $[M-H^+]^-$
P-2004				439.1
P-2005				435.1
P-2006				444.1
P-2007				437.4 439.5
P-2008				428.1 430.1
P-2009				523.3 $[M-H^+]^-$
P-2010				539.3 541.3 $[M-H^+]^-$
P-2011				530.0 532.4

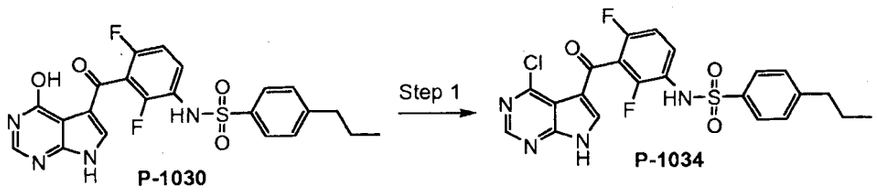
P-2012				463.8
P-2013				479.1
P-2014				581.4
P-2015				447.9
P-2016				549.9
P-2017				481.9

* During the reaction, the 4-chloro was also displaced by methanol to form the 4-methoxy analog in step 1 in the synthesis of **P-2004**, which is carried through step 2 to form **P-2005**.

Example 6: Synthesis of N-[3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide P-1034.

[0265] N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide **P-1034** is synthesized in one step from N-[2,4-difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide **P-1030** as shown in Scheme 6.

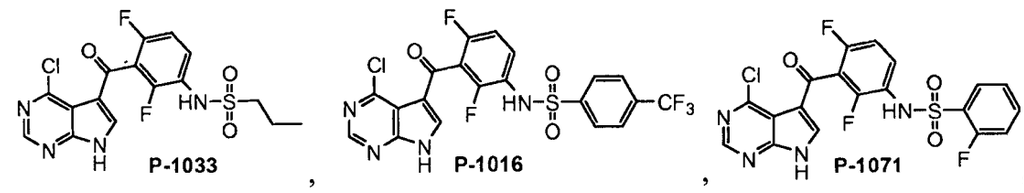
Scheme 6



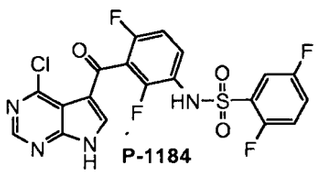
*Step 1 - Preparation of N-[3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1034**):*

[0266] To N-[2,4-difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1030**, 239 mg, 0.506 mmol), phosphoryl chloride (4.0 mL, 43 mmol) is added and the suspension is heated in an oil bath at 100 °C for one hour. The reaction is allowed to cool, then poured onto ice. The resulting solid is collected by vacuum filtration and dried to provide the desired compound (**P-1030**, 218 mg). MS (ESI) $[M+H^+]^+ = 490.9$.

[0267] Propane-1-sulfonic acid [3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide **P-1033** and N-[3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide **P-1016**, N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide **P-1071**, and N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide **P-1184**,



, and

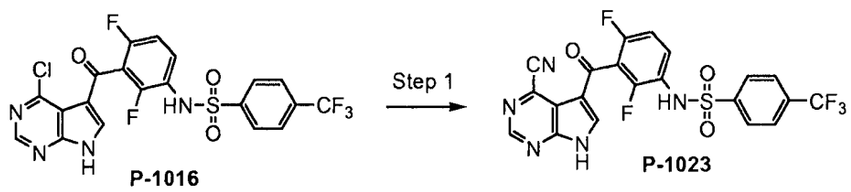


are prepared similarly to the protocol of Scheme 6 from propane-1-sulfonic acid [2,4-difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide **P-1022**, N-[2,4-difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide **P-1012**, N-[2,4-difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide **P-1070**, and N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide **P-1183**, respectively. MS (ESI) $[M+H^+]^+ = 414.8$ (**P-1033**), 516.9 (**P-1016**), 466.9, 468.9 (**P-1071**), and 484.9, 486.9 (**P-1184**).

Example 7: Synthesis of N-[3-(4-cyano-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide P-1023.

[0268] N-[3-(4-cyano-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide **P-1023** is synthesized in one step from N-[3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide **P-1016** as shown in Scheme 7.

Scheme 7



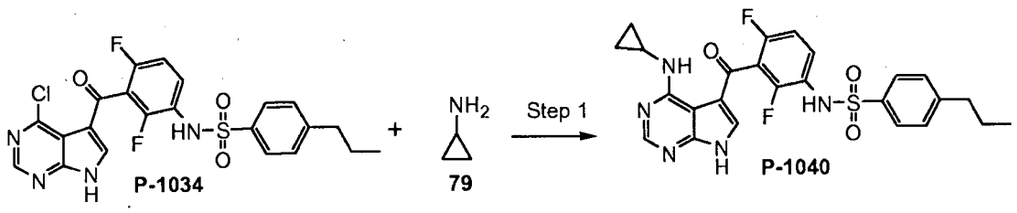
*Step 1 - Preparation of N-[3-(4-cyano-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1023**):*

[0269] To N-[3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1016**, 62 mg, 0.12 mmol), 1.00 mL of dimethyl sulfoxide is added, followed by potassium cyanide (39.0 mg, 0.60 mmol). The reaction is heated at 150 °C in an oil bath for 4 hours, then at 150 °C overnight. The reaction is poured into water and extracted with ethyl acetate. The organic layer is concentrated under vacuum and purified by silica gel column chromatography, eluting with a gradient of 10-60% ethyl acetate in hexanes. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**P-1023**, 8 mg). MS (ESI) $[M+H^+]^+ = 508.1$.

Example 8: Synthesis of N-[3-(4-cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide P-1040.

[0270] N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide **P-1040** is synthesized in one step from N-[3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide **P-1034** as shown in Scheme 8.

Scheme 8



*Step 1 - Preparation of N-[3-(4-cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1040**):*

[0271] To N-[3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1034**, 50 mg, 0.10 mmol), 0.702 mL of isopropyl alcohol is added, followed by cyclopropylamine (**79**, 0.0357 mL, 70% aqueous solution, 0.509 mmol). The reaction is heated at 80 °C in an oil bath for 17 hours, then poured into water and brine and extracted with ethyl acetate. The organic layer is dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum to provide the desired compound (**P-1040**, 52 mg). MS (ESI) $[M+H^+]^+ = 512.0$.

[0272] Additional compounds are prepared following the protocol of Scheme 8. In some instances, without limitation, the 4-chloro-7H-pyrrolo[2,3-d]pyrimidine compound (or similar 4-halogen substituted 1H-pyrrolo[2,3-b]pyridine compound) is reacted directly in the liquid amine compound without additional solvent (e.g. isopropyl alcohol). In some instances, without limitation, the reaction mixture includes triethylamine. Compounds may be further purified by standard techniques, such as silica gel chromatography or HPLC. Compounds are prepared optionally substituting N-[3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide **P-1034** with a suitable 4-chloro-7H-pyrrolo[2,3-d]pyrimidine or 4-halo-1H-pyrrolo[2,3-b]pyridine compound and optionally substituting cyclopropylamine **79** with a suitable amine in step 1. The following compounds are made using this procedure:

N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1013**),

N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1020**),

N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1024**),

N-[2,4-Difluoro-3-(4-methylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1026**),

N-[3-(4-Amino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-

benzenesulfonamide (**P-1031**),
N-[2,4-Difluoro-3-(4-propylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1032**),
N-[2,4-Difluoro-3-(4-phenylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1037**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1039**),
Propane-1-sulfonic acid [3-(4-cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1041**),
N-{2,4-Difluoro-3-[4-(2-hydroxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1043**),
N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-1046**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(tetrahydro-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1047**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-phenylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1048**),
N-[3-(4-Dimethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1049**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1050**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1051**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1052**),
N-{2,4-Difluoro-3-[4-(tetrahydro-furan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1054**),
N-[2,4-Difluoro-3-(4-isopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1055**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-1056**),
N-{2,4-Difluoro-3-[4-(1-methyl-piperidin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1057**),

N-{2,4-Difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1058**),

N-{3-[4-(2-Dimethylamino-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1059**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(oxetan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1060**),

N-[2,4-Difluoro-3-(4-pyrrolidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1061**),

N-{2,4-Difluoro-3-[4-(1-methyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1062**),

N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1063**),

N-[2,4-Difluoro-3-(4-hydroxyamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1064**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(4-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1065**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-hydrazino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1066**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(naphthalen-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1067**),

Propane-1-sulfonic acid (2,4-difluoro-3-{4-[(oxetan-3-ylmethyl)-amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1068**),

N-{2,4-Difluoro-3-[4-(4-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1069**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(naphthalen-1-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1072**),

Propane-1-sulfonic acid [3-(4-benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1074**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-propylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1075**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(pyridin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1076**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-

carbonyl]-phenyl}-amide (**P-1077**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1078**),

Propane-1-sulfonic acid {3-[4-(cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1079**),

Propane-1-sulfonic acid {3-[4-(1-benzyl-pyrrolidin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1080**),

Propane-1-sulfonic acid [3-(4-cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1081**),

Propane-1-sulfonic acid [3-(4-ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1082**),

Propane-1-sulfonic acid {3-[4-(3-dimethylamino-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1083**),

Propane-1-sulfonic acid {3-[4-(3-chloro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1084**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1085**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1086**),

Propane-1-sulfonic acid {3-[4-(4-chloro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1087**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1088**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(4-trifluoromethyl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1089**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(6-methoxy-pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1090**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-trifluoromethyl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1091**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1092**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-p-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1093**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-fluoro-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1094**),
Propane-1-sulfonic acid {3-[4-(1-ethyl-piperidin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1095**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1-methanesulfonyl-piperidin-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1096**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(tetrahydro-furan-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1097**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-methylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1098**),
Propane-1-sulfonic acid {3-[4-(1-ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1099**),
Propane-1-sulfonic acid {3-[4-(1,3-dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1100**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(2-fluoro-4-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1101**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1-methyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1102**),
N-[3-(4-Cyclopropylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1103**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-fluoro-5-methoxy-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1105**),
Propane-1-sulfonic acid {3-[4-(benzo[1,2,5]thiadiazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1134**),
N-[3-(4-Benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1135**),
N-{2,4-Difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1136**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1137**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1138**),
N-{2,4-Difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2,5-

difluoro-benzenesulfonamide (**P-1139**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1140**),
N-[2,4-Difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1141**),
N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1142**),
N-{3-[4-(1,3-Dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-1143**),
N-[3-(4-Benzylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1144**),
N-{2,4-Difluoro-3-[4-(pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1145**),
N-{3-[4-(Cyclopropylmethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1146**),
N-[3-(4-Cyclopentylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1147**),
N-[3-(4-Ethylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1148**),
N-{2,4-Difluoro-3-[4-(3-methoxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1149**),
N-{2,4-Difluoro-3-[4-(2-methoxy-ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-2-fluoro-benzenesulfonamide (**P-1150**),
N-[2,4-Difluoro-3-(4-isobutylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1151**),
N-[2,4-Difluoro-3-(4-m-tolylamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1152**),
N-{3-[4-(1-Ethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1153**),
N-{3-[4-(1,3-Dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-2-fluoro-benzenesulfonamide (**P-1154**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1H-indazol-6-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1157**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(1H-indazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1158**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(4-hydroxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1159**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[(5-methyl-1H-pyrazol-3-ylmethyl)-amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1160**),
3-({5-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino}-methyl)-benzoic acid (**P-1161**),
4-{5-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino}-benzoic acid methyl ester (**P-1162**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-[1,2,4]triazol-1-yl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1164**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-oxazol-5-yl-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1165**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[(pyridin-3-ylmethyl)-amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1166**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-[1,2,4]triazol-1-yl-propylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1167**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-pyridin-3-yl-propylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1168**),
Propane-1-sulfonic acid {2,4-difluoro-3-[4-(3-hydroxy-phenylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1169**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(5-methyl-4H-[1,2,4]triazol-3-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1170**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(5-methyl-tetrazol-1-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1171**),
Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(4H-[1,2,4]triazol-3-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1172**),
Propane-1-sulfonic acid (3-{4-[(benzo[1,2,5]oxadiazol-5-ylmethyl)-amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-2,4-difluoro-phenyl)-amide (**P-1173**),
Propane-1-sulfonic acid {3-[4-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1174**),
Propane-1-sulfonic acid {3-[4-(1,1-dioxo-tetrahydro-1lambda*6*-thiophen-3-ylamino)-7H-pyrrolo[2,3-

d]pyrimidine-5-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1175**),

Propane-1-sulfonic acid (2,4-difluoro-3-{4-[2-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1176**),

Propane-1-sulfonic acid {2,4-difluoro-3-[4-(2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-amide (**P-1177**),

Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(2-methyl-2H-tetrazol-5-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1178**),

Propane-1-sulfonic acid (2,4-difluoro-3-{4-[3-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenylamino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1179**),

Propane-1-sulfonic acid (2,4-difluoro-3-{4-[(pyridazin-4-ylmethyl)-amino]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-phenyl)-amide (**P-1180**),

N-{3-[4-(Cyclopropylmethyl-amino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-2018**),

N-{3-[4-(Cyclopropylmethyl-amino)-5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-2019**),

N-{3-[5-Cyano-4-(cyclopropylmethyl-amino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-2020**),

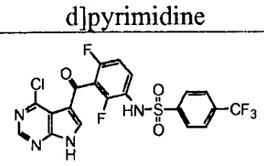
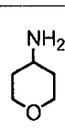
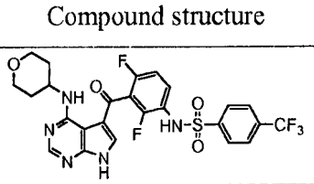
N-{3-[5-Chloro-4-(cyclopropylmethyl-amino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-2021**),

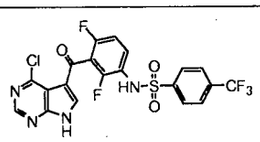
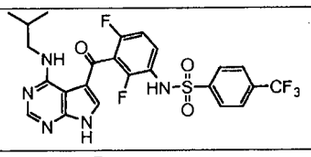
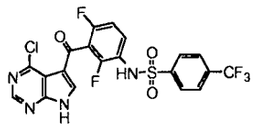
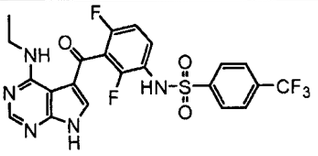
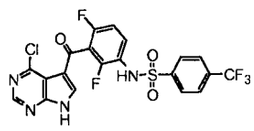
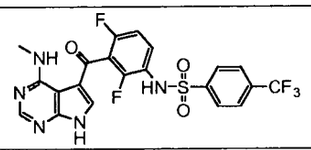
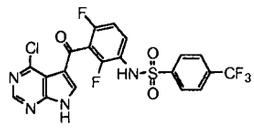
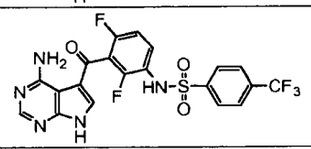
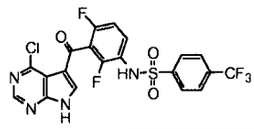
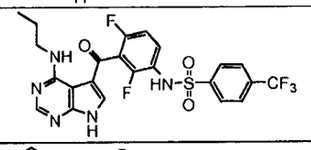
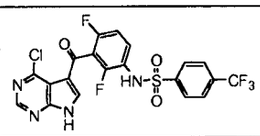
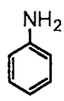
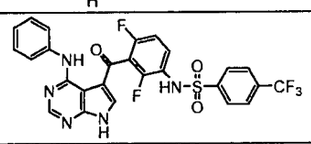
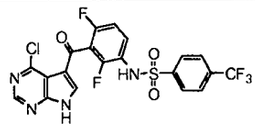
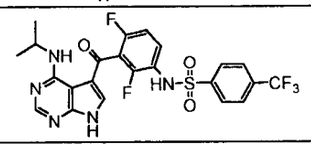
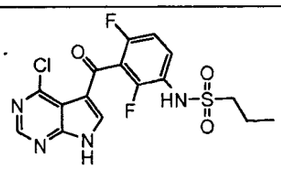
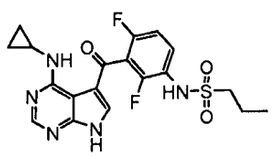
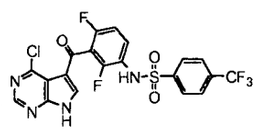
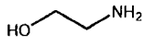
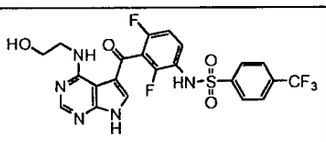
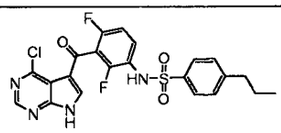
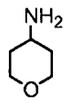
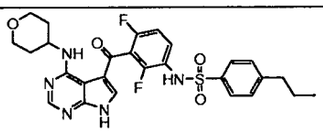
N-{3-[4-(Cyclopropylmethyl-amino)-5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-2022**),

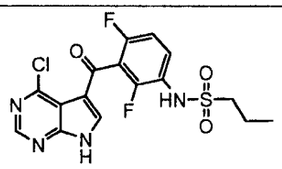
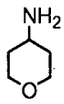
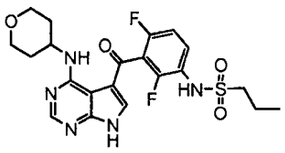
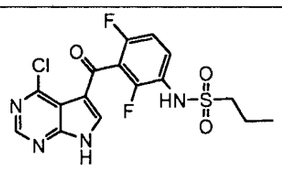
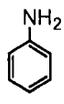
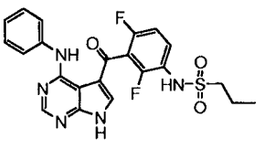
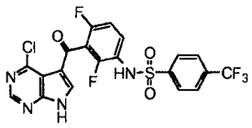
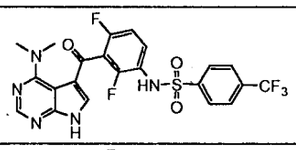
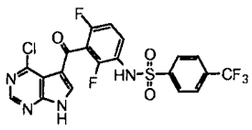
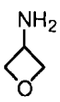
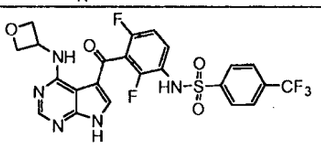
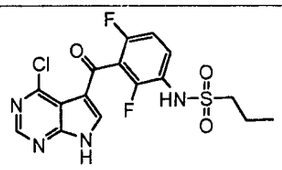
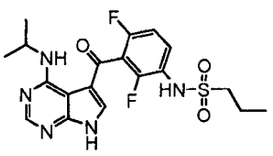
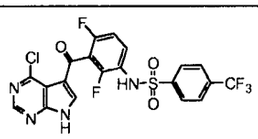
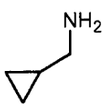
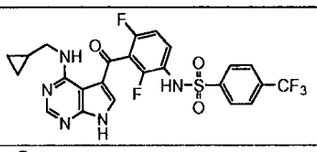
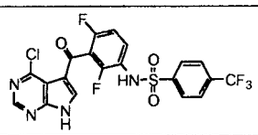
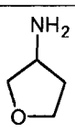
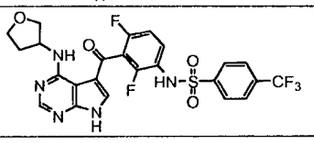
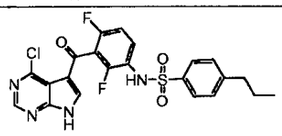
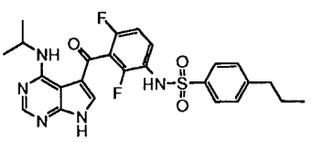
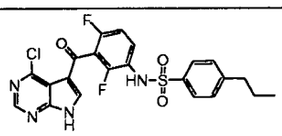
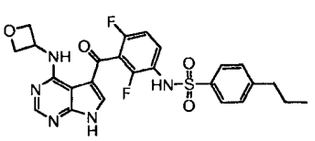
N-{3-[4-(Cyclopropylmethyl-amino)-5-hydroxymethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-2023**),

N-{3-[4-(Cyclopropylmethyl-amino)-5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-2,5-difluoro-benzenesulfonamide (**P-2024**).

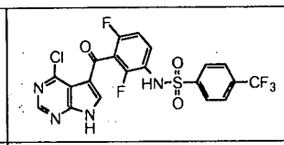
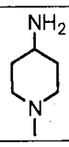
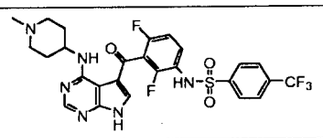
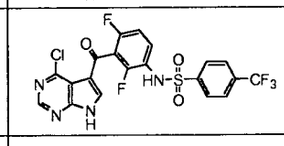
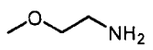
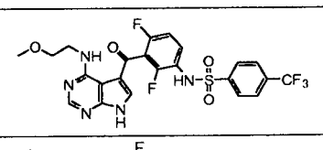
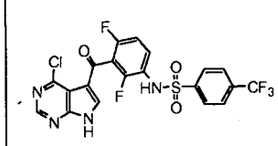
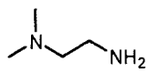
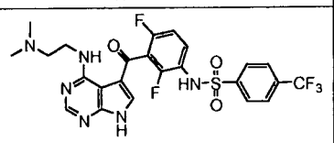
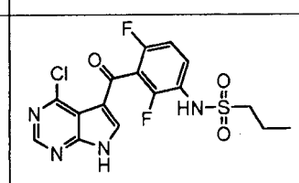
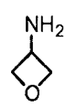
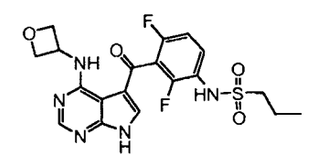
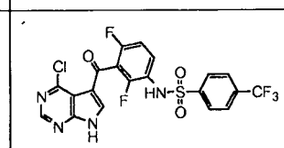
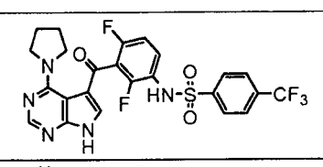
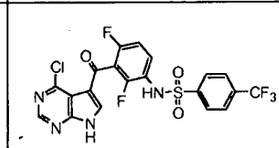
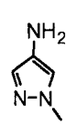
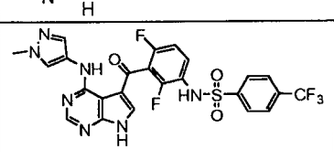
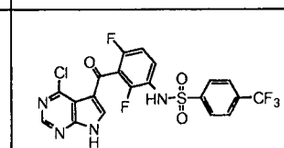
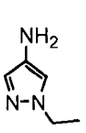
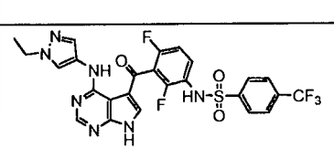
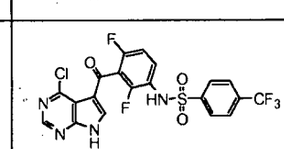
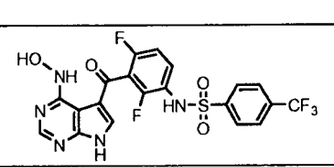
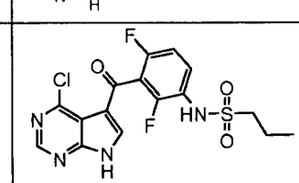
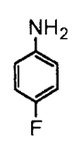
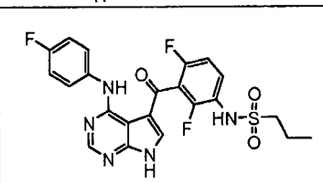
The following table indicates the 4-chloro-7H-pyrrolo[2,3-d]pyrimidine compound or 1H-pyrrolo[2,3-b]pyridine (column 2) and amine compound (column 3) used in step 1 to afford the desired compound (column 4). The compound number is provided in column 1, and the observed mass is in column 5.

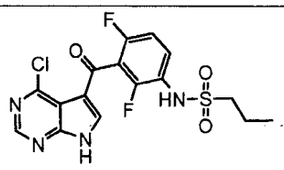
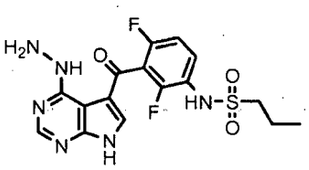
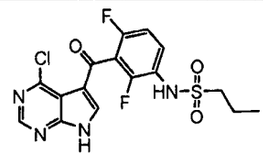
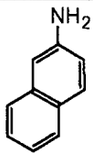
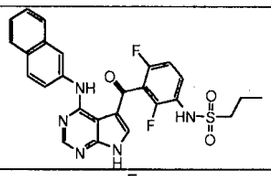
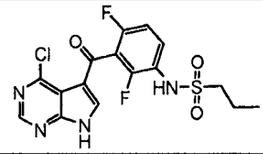
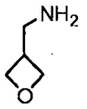
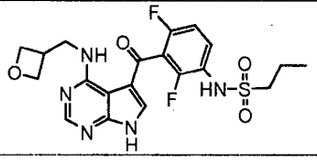
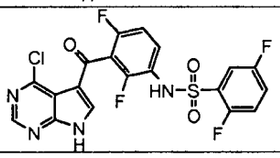
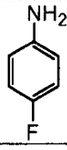
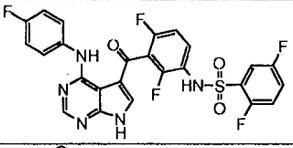
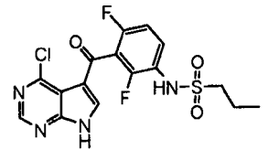
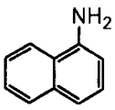
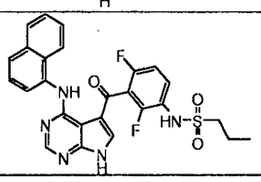
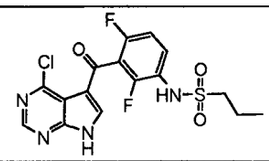
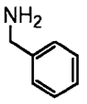
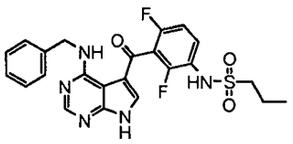
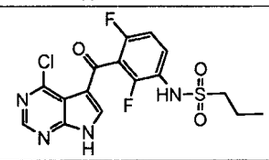
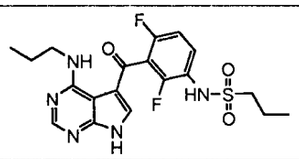
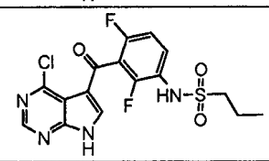
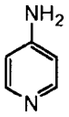
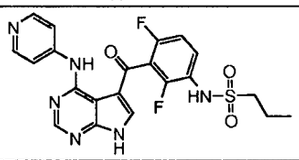
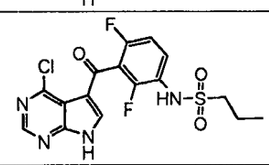
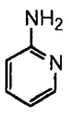
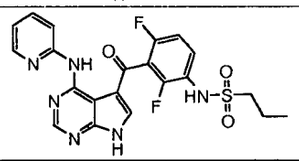
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P-1013				582.0

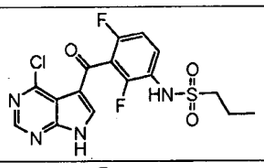
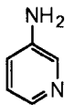
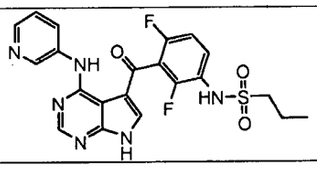
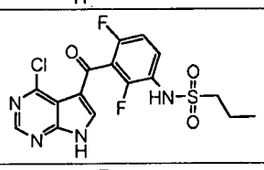
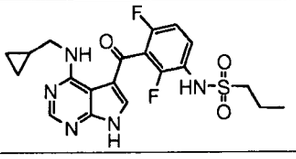
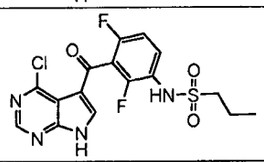
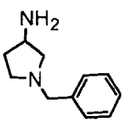
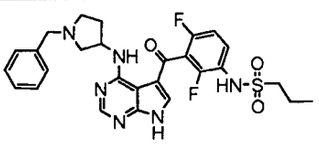
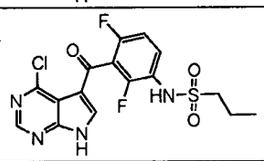
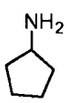
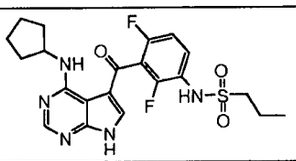
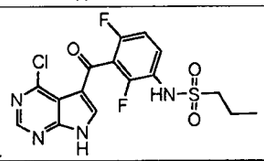
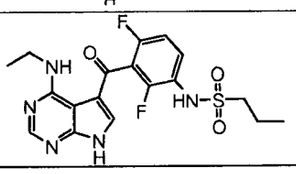
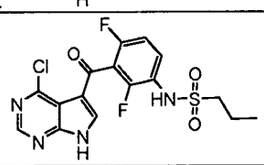
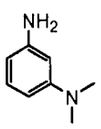
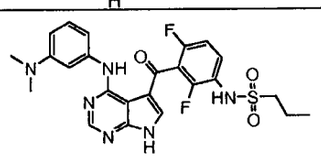
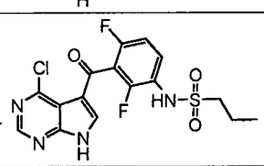
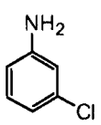
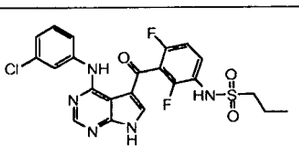
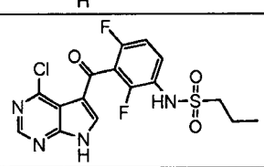
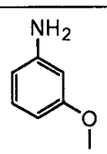
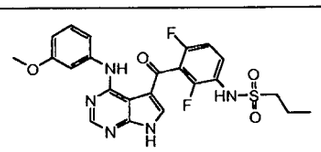
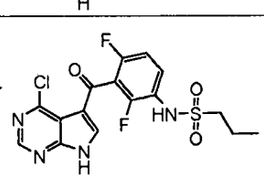
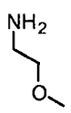
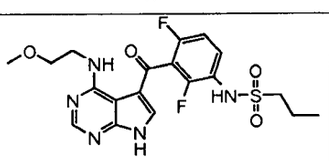
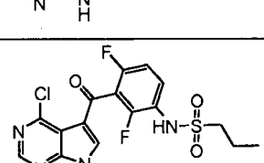
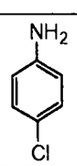
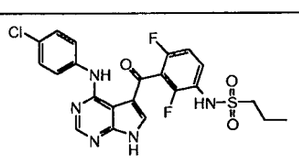
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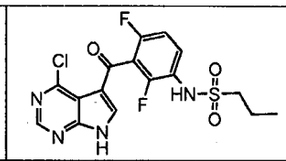
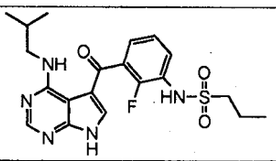
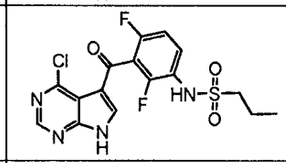
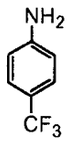
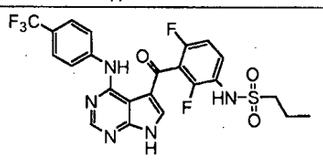
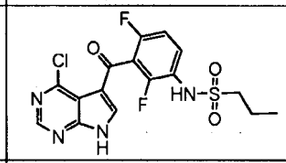
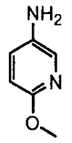
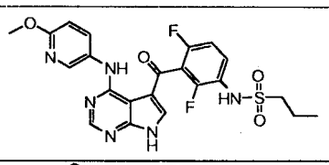
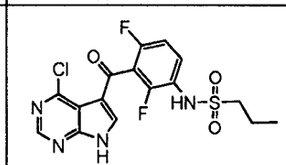
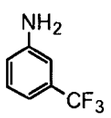
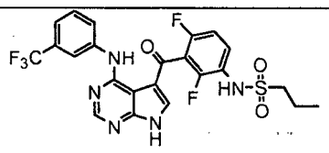
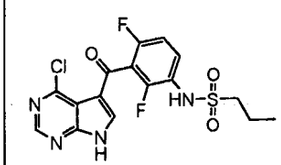
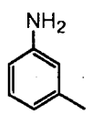
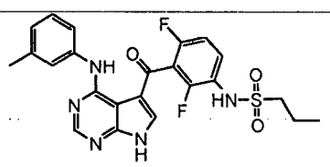
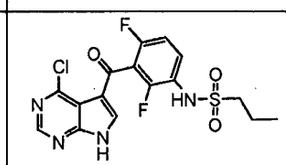
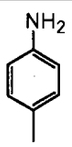
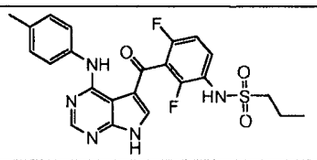
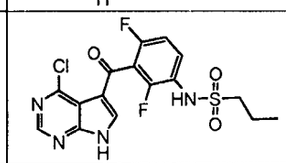
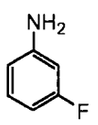
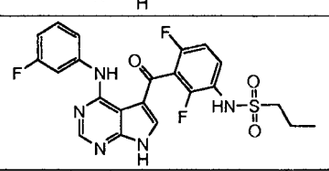
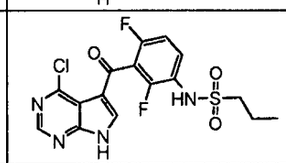
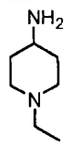
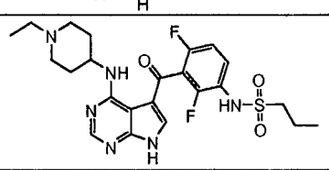
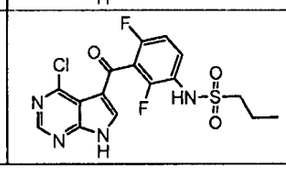
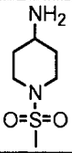
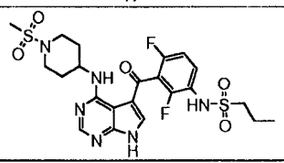
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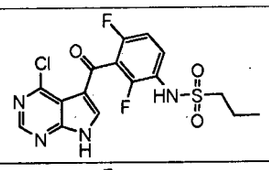
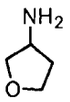
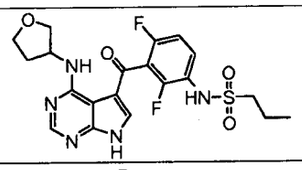
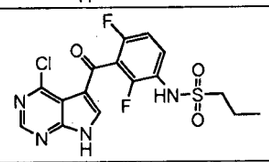
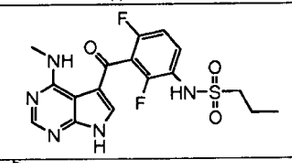
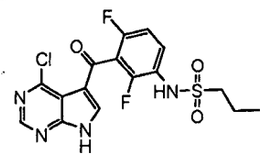
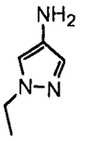
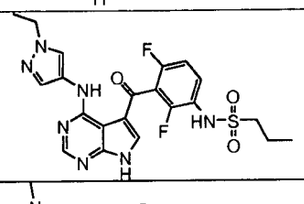
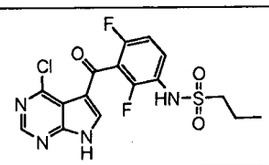
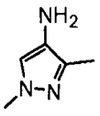
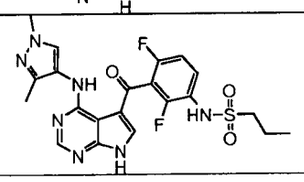
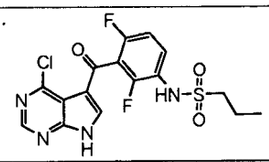
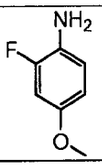
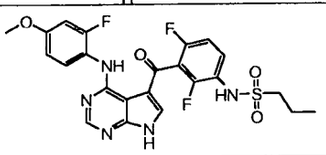
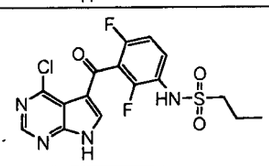
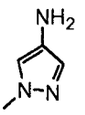
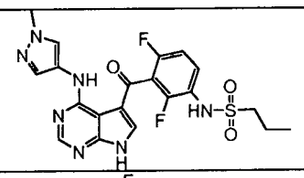
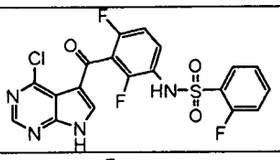
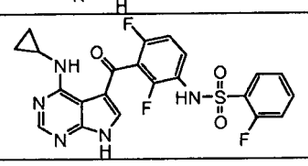
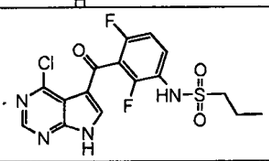
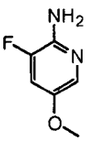
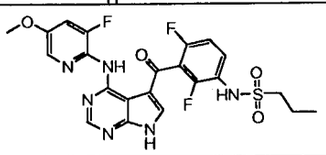
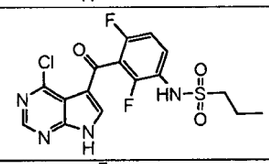
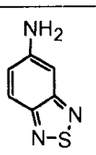
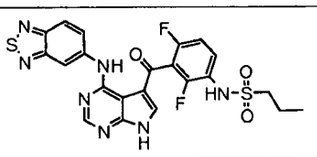
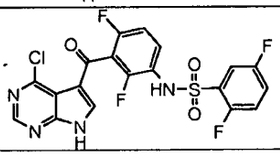
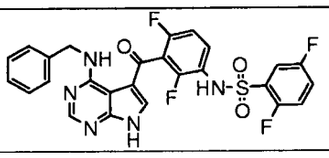
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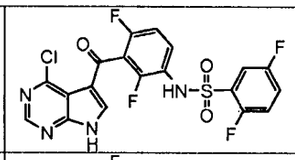
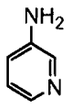
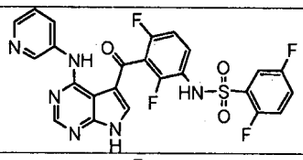
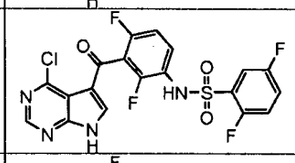
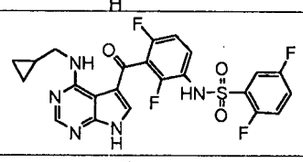
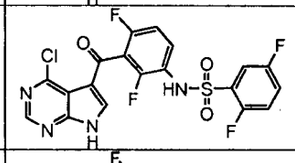
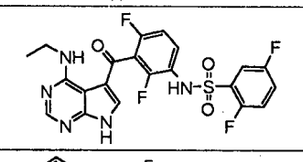
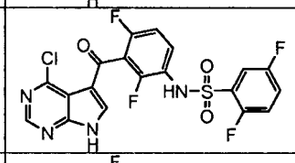
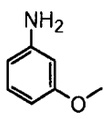
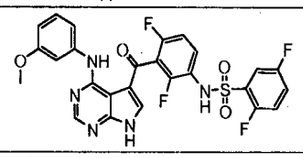
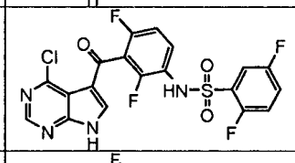
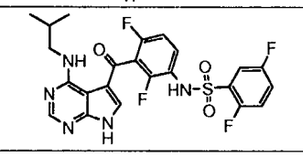
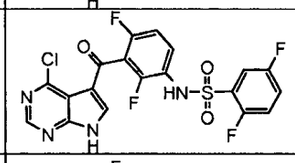
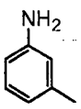
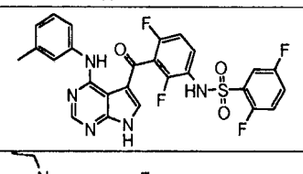
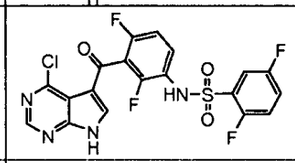
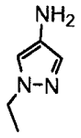
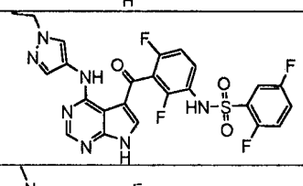
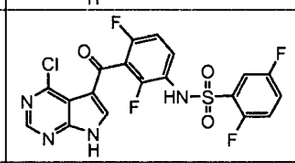
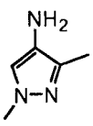
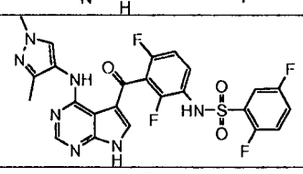
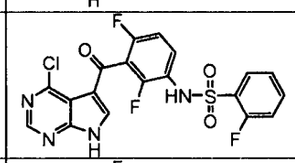
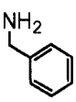
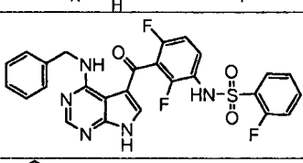
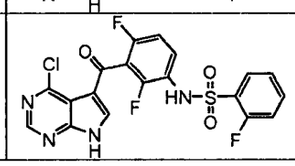
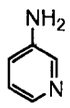
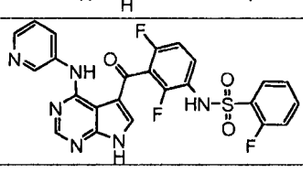
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P-1058				556.3
P-1059				569.5
P-1060				451.95
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P-1064		H_2N–OH		513.9
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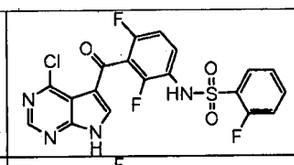
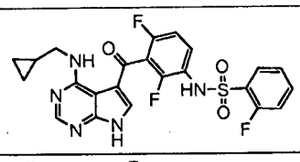
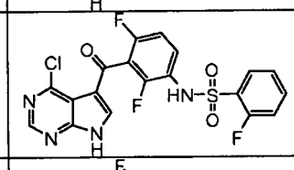
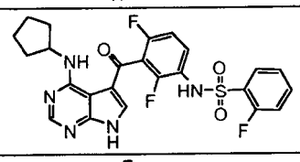
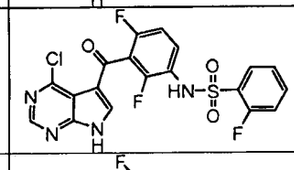
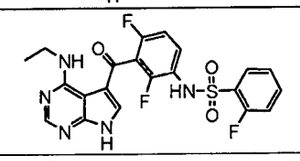
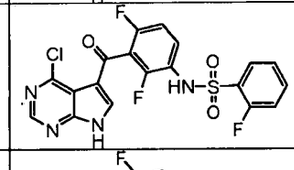
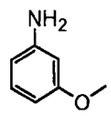
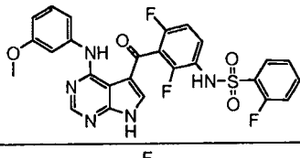
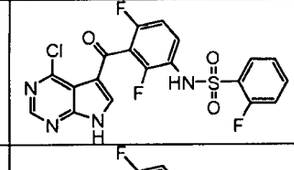
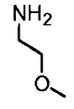
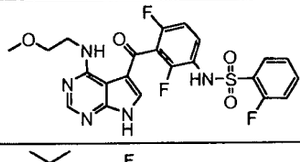
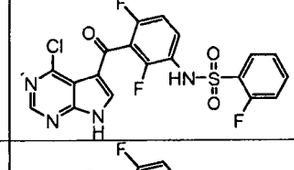
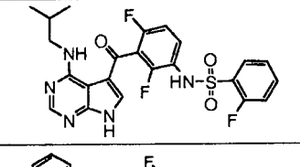
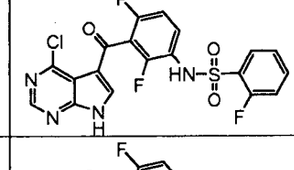
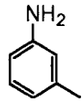
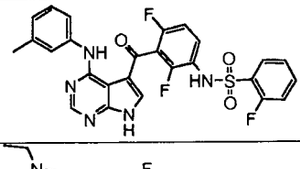
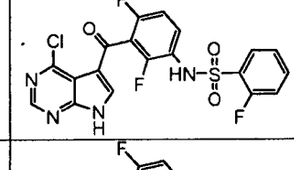
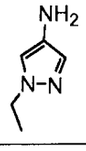
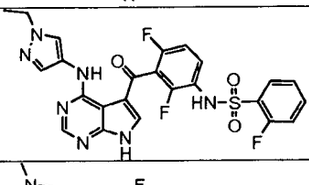
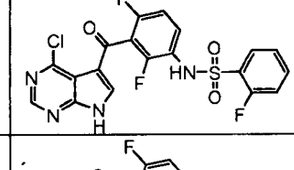
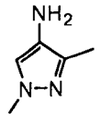
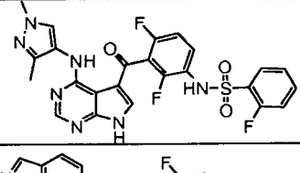
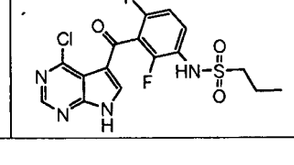
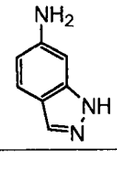
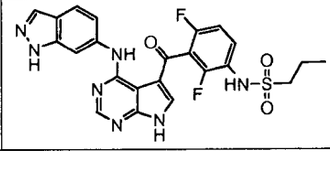
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P-1067				522.25
P-1068				513.9 $[M-H^+]^-$
P-1069				559.9
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P-1074				486.5
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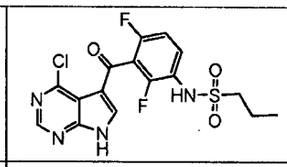
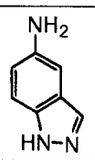
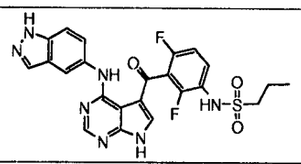
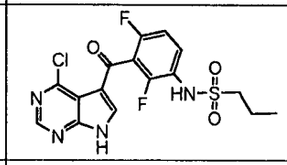
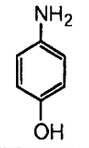
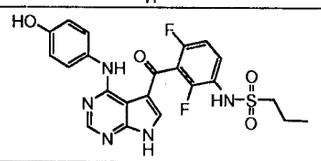
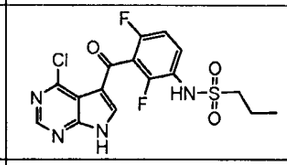
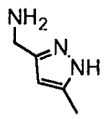
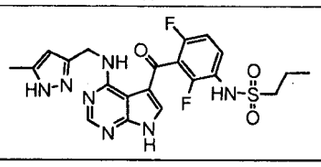
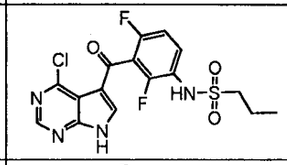
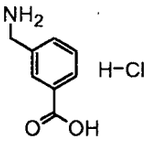
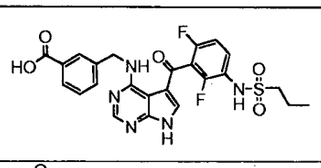
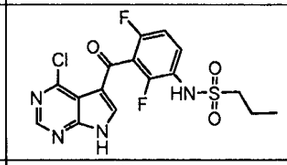
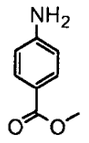
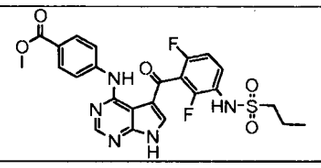
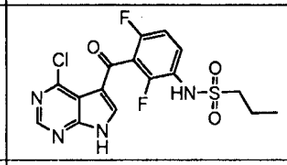
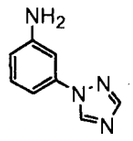
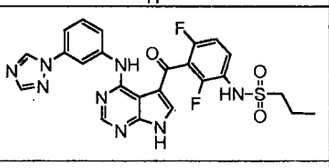
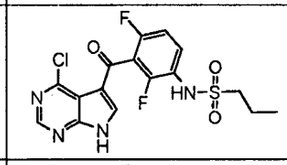
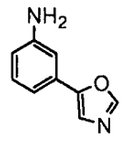
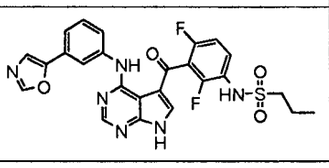
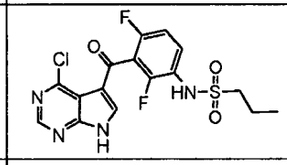
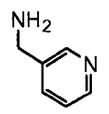
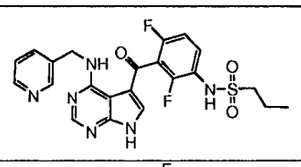
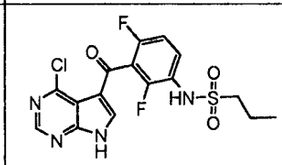
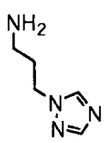
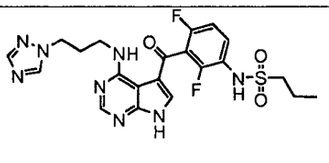
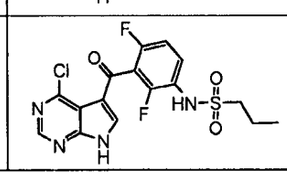
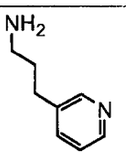
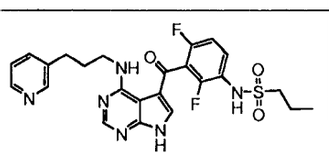
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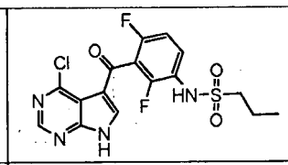
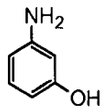
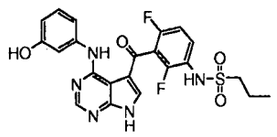
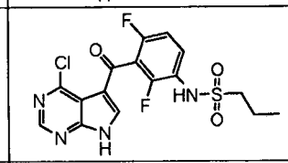
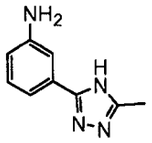
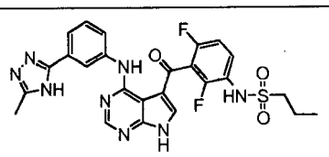
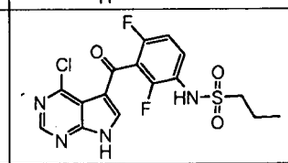
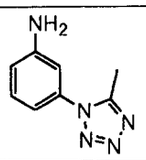
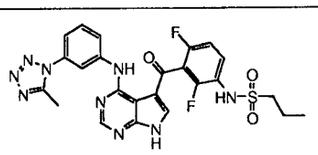
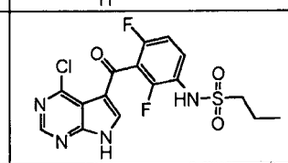
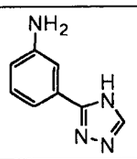
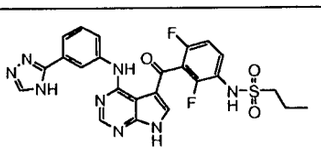
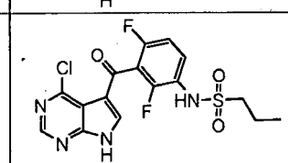
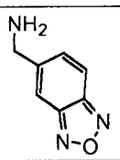
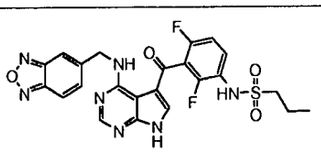
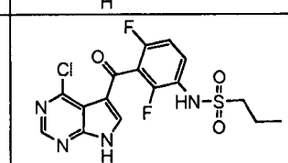
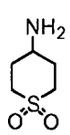
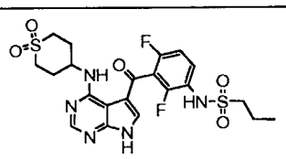
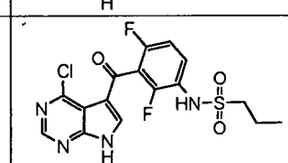
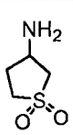
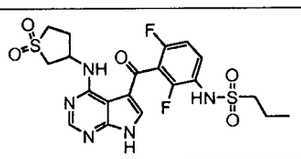
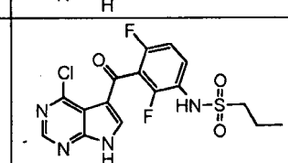
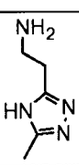
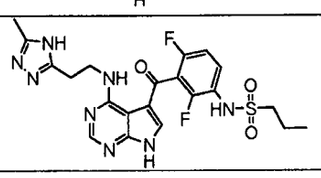
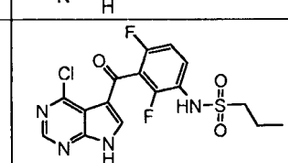
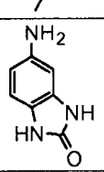
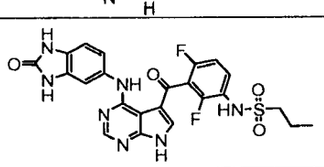
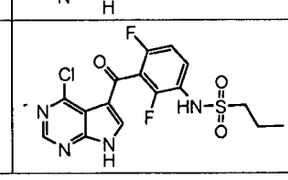
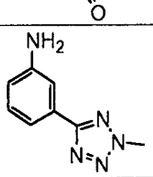
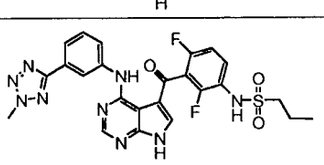
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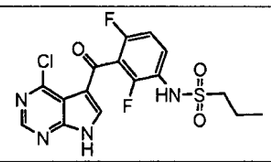
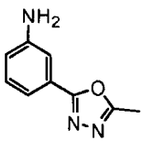
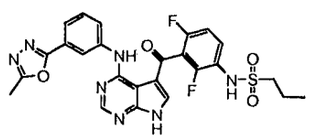
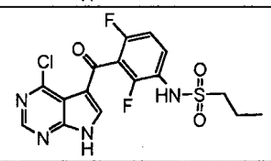
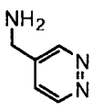
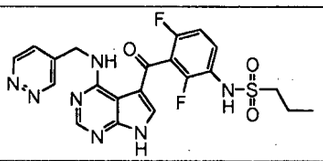
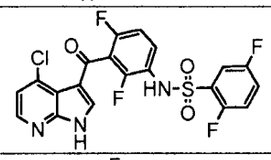
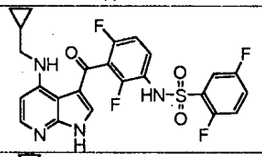
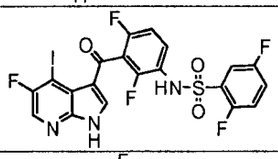
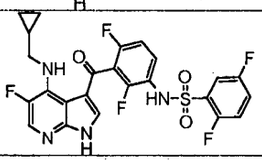
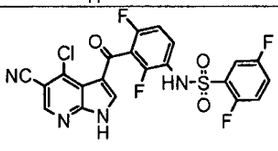
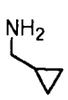
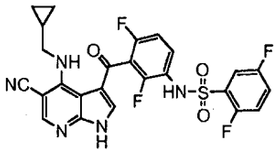
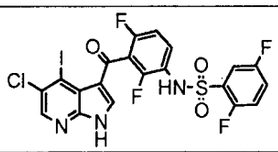
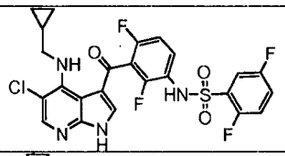
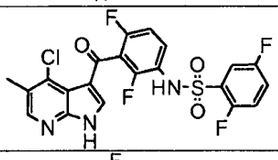
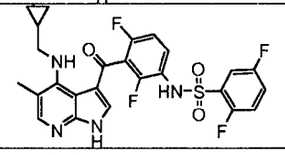
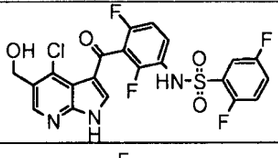
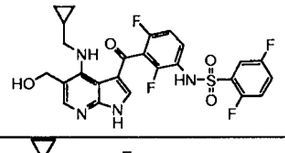
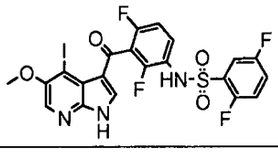
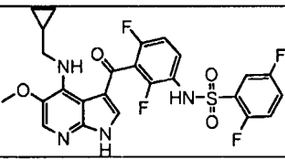
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P-1098				410.0
P-1099				490.5
P-1100				490.5
P-1101				520.5
P-1102				476.0
P-1103				488.0
P-1105				521.0
P-1134				530.0
P-1135				556.0

P-1136				543.5
P-1137				520.5
P-1138				494.0
P-1139				572.0
P-1140				522.0
P-1141				556.0
P-1142				560.0
P-1143				560.0
P-1144				538.5
P-1145				525.5

P-1146				502.0
P-1147				516.5
P-1148				476.0
P-1149				554.0
P-1150				506.0
P-1151				504.0
P-1152				538.5
P-1153				542.0
P-1154				542.0
P-1157				512.0

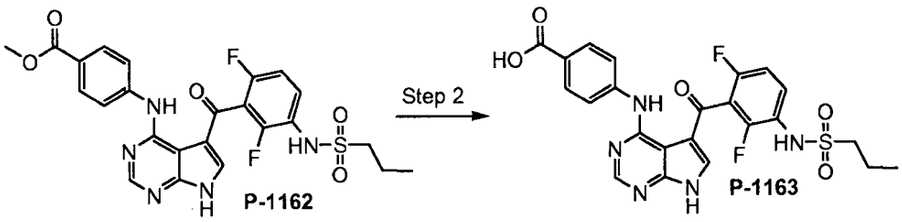
P-1158				512.0
P-1159				489.1
P-1160				488.0 $[M-H^+]^-$
P-1161				530.0
P-1162				530.0
P-1164				539.5
P-1165				539.5
P-1166				487.5
P-1167				505.0
P-1168				515.5

P-1169				488.0
P-1170				553.5
P-1171				554.0
P-1172				539.5
P-1173				528.0
P-1174				528.0
P-1175				514.5
P-1176				505.0
P-1177				528.0
P-1178				554.0

P-1179				554.0
P-1180				488.0
P-2018*				
P-2019				535.1 $[M-H^+]^-$
P-2020				544.0 $[M-H^+]^-$
P-2021				
P-2022*				
P-2023*				
P-2024*				

* Palladium catalyst was used to facilated the coupling reaction.

[0273] 4-{5-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino}-benzoic acid **P-1163** is prepared from 4-{5-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino}-benzoic acid methyl ester **P-1162** by the following Step 2.



*Step 2 - Preparation of 4-{5-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino}-benzoic acid (**P-1163**):*

[0274] 4-{5-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino}-benzoic acid methyl ester (**P-1162**, 26 mg, 0.05 mmol) is combined with 1 mL of methanol is added, 0.5 mL of tetrahydrofuran, and 0.5 mL of 2 M sodium hydroxide. The reaction is stirred at room temperature for 48 hours, then neutralized with 1 M hydrochloric acid and the volatile solvents are removed under vacuum. The remaining aqueous suspension is filtered to collect the solids, which are dried under vacuum to provide the desired compound (**P-1163**, 25 mg). MS (ESI) $[M+H^+]^+ = 516.0$.

Example 9: Compound properties

[0275] 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. In addition to demonstrating kinase inhibitory activity against any or all of B-Raf, c-Raf-1 and B-Raf V600E in both biochemical and cell based assays, compounds may show favorable solubility, favorable pharmacokinetic properties, and low Cyp inhibition. The compounds are assessed in the following assays or similar assays available to one skilled in the art.

[0276] 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 kinase activity, c-Raf-1 kinase activity, or B-Raf V600E 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}.

[0277] 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) are used in such assays. 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.

[0278] 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.

[0279] 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.

[0280] On day 2, compound at a maximum concentration of 5 mM is serially diluted 1:3 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.

[0281] 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.

[0282] 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. Results for compounds that are tested and show substantially no inhibition below the highest tested concentration are represented as "-"

in the tables below. 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.

[0283] The following table provides data indicating the B-Raf, B-Raf V600E and c-Raf-1 biochemical inhibitory activity and corresponding activity ratios for exemplary compounds as described herein:

Compound number	Biochemical activity (IC_{50} μM)			Biochemical activity ratio		
	B-Raf	V600E	c-Raf-1	B/C	V600E/C	B/V600E
P-1001	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1002	> 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1003	> 0.1	< 0.1	< 0.1	> 10	0.1-10	> 10
P-1004	> 0.1	< 0.1	< 0.1	> 10	0.1-10	> 10
P-1005	> 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1006	> 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1007	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1008	> 0.1	> 0.1	> 0.1	0.1-10	0.1-10	0.1-10
P-1009	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1010	> 0.1	> 0.1	> 0.1	0.1-10	> 10	0.1-10
P-1011	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1012	> 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1013	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1014	> 0.1	> 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1015	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1016	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1017	> 0.1	> 0.1	> 0.1	0.1-10	> 10	0.1-10
P-1018	> 0.1	> 0.1	> 0.1	> 10	0.1-10	> 10
P-1019	> 0.1	> 0.1	> 0.1	0.1-10	0.1-10	0.1-10
P-1020	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1021	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1022	> 0.1	> 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-1023	> 0.1	> 0.1	> 0.1	0.1-10	> 10	0.1-10
P-1024	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1025	> 0.1	> 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1026	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1027	> 0.1	> 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1028	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1029	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1030	> 0.1	> 0.1	< 0.1	0.1-10	> 10	< 0.1
P-1031	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1032	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-1033	> 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1034	> 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1035	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-1036	> 0.1	< 0.1	< 0.1	> 10	0.1-10	> 10
P-1037	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1038	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1039	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10

P-1040	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1041	< 0.1	< 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-1042	< 0.1	< 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1043	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1044	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1045	> 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1046	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1047	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-1048	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-1049	> 0.1	> 0.1	> 0.1	> 10	> 10	0.1-10
P-1050	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-1051	< 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1052	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-1053	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1054	< 0.1	< 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1055	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1056	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1057	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1058	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1059	> 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1060	< 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1061	> 0.1	> 0.1	> 0.1	0.1-10	> 10	0.1-10
P-1062	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-1063	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-2001	< 0.1	< 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-2002	< 0.1	< 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-2003	< 0.1	< 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-2004	< 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-2005	< 0.1	< 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-2006	< 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-2007	< 0.1	< 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-2008	< 0.1	< 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-2009	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-2010	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-2011	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-2012	> 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-2013	> 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-2014	> 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-2015	> 0.1	> 0.1	< 0.1	> 10	0.1-10	> 10
P-2016	> 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-2017	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10

[0284] As an indication of relative solubility, the turbidity of compounds in aqueous solutions is assessed. To assess possible compound properties in different physiological compartments, such as stomach, intestine, and blood, a series of aqueous buffers with varying pH is used. Thus each compound

is diluted into four different physiologically relevant buffers and solution turbidity is measured by spectrophotometry. The concentration of compound that demonstrates turbidity by forming enough insoluble suspension to raise the average optical density above 0.01 at three wavelengths (490, 535, and 650 nm) is used to define the limit of the compound solubility in that buffer.

[0285] Compounds are dissolved at a concentration of 25 mM in dimethyl sulfoxide, then serially diluted 1:1 into a 96 well plate, diluting 10 times in pure dimethyl sulfoxide, with the final well of each row a dimethyl sulfoxide blank. In an assay plate, 99 μL of appropriate buffer is added to each well, and 1 μL of each sample dilution is added to the buffer, achieving a range of final total concentrations in aqueous solutions having different pH. The buffers used are Simulated Gastric Fluid (SGF-pH 1.5) 0.5M NaCl, pH 1.5; Simulated Intestinal fluid (SIF-pH 4.5 and pH 6.8) 0.05M NaH_2PO_4, pH 4.5 and 6.8; and Hepes Buffer (HEPES-pH 7.4) 10 mM HEPES, 150 mM NaCl, pH 7.4. Control compounds pyrene, estriol and propranolol HCl are also assessed. Plates are spun and then mixed for 1 minute, and the absorbance is read using a Tecan Safire II to read wavelengths in the visible range (490, 535, and 650 nm) at four locations per well, reflecting the degree of turbidity present. The average optical density for each wavelength in each well is graphed vs. compound concentration, and the concentration at which the curve crosses a threshold O.D. of 0.01 for each wavelength is reported as the endpoint turbidity assay result. The average of the three wavelengths is used to compare turbidity of compounds. Compounds are considered to have low solubility if the threshold concentration is <31.3 μM, moderate solubility if the threshold concentration is 31.3 μM to 250 μM, and high solubility if the threshold concentration is >250 μM.

[0286] The following table indicates the relative solubility (L = low, M = moderate, H = high) based on turbidity threshold concentration at each pH for exemplary compounds according to the invention as indicated:

Compound number	turbidity threshold (L, M, H)			
	1.4	4.5	6.8	7.4
P-1001	H	M	M	M
P-1002	H	H	H	H
P-1003	H	M	M	M
P-1004	H	H	H	H
P-1005	H	L	L	L
P-1006	L	L	L	H
P-1007	L	L	L	L
P-1008	M	M	L	M
P-1009	H	L	L	M
P-1010	L	L	L	M
P-1011	M	L	L	L

P-1012	M	M	H	H
P-1013	L	L	L	M
P-1014	M		M	M
P-1016	L		L	H
P-1020	H			H
P-1024	M	L	L	L
P-1025	M	L	M	
P-1026			M	M
P-1027		L	M	
P-1028	M	L	L	M
P-1029	M			M
P-1030		M		M
P-1031	M	M	M	M
P-1032	L	L		
P-1033	H	H	H	H
P-1034	M	M	M	M
P-1035	L	L	L	L
P-1037	L	L	L	L
P-1039	M	M	M	M
P-1040	M	L	L	L
P-1041	H	M	M	M
P-1042	M	L	L	L
P-1043	H	M	M	M
P-1044	M	M	M	M
P-1045	M	L	L	L
P-1046	M	L	L	L
P-1047	M	L	L	L
P-1048	M	M	M	M
P-1049	M	M	M	M
P-1050	H	M	M	M
P-1051	H	M	M	M
P-1052	L	L	L	L
P-1053	L	L	L	L
P-1054	M	L	L	L
P-1055	L	L	L	L
P-1056	M	L	L	L
P-1057	H	H	M	M
P-1058	M	L	L	L
P-1059	H	M	M	M
P-1060	H	M	H	H
P-1061	H	M	M	H
P-1062	L	L	L	L
P-1063	L	L	L	L
P-1073	M	L	L	L
P-1076	H	H	H	H
P-1077	H	L	L	L
P-1078	M	L	L	L

P-1079	M	L	L	L
P-1081	H	L	L	L
P-1084	M	M	M	M
P-1085	L	L	L	L
P-1087	M	L	M	M
P-1088	M	L	L	L
P-1094	L	L	M	L
P-1095	H	H	H	H
P-1099	M	L	M	M
P-1100	M	M	L	L
P-1101	L	L	L	L
P-1103	M	L	L	M
P-1104	H	M	M	M
P-1107	M	L	M	M
P-1143	L	L	L	L
P-1154	L	L	L	L
P-2001	M	M	M	M
P-2002	M	M	M	M
P-2003	M	M	M	M
P-2004	L	L	L	L
P-2005	M	L	L	M
P-2006	M	M	M	M
P-2007	M	M	M	M
P-2008	L	M	L	M
P-2009	L	M	M	M
P-2010	L	L	L	M
P-2011	L	L	L	L
P-2013	H	H	H	H
P-2014	L	L	L	L
P-2015	M	M	M	M
P-2016	L	L	L	M
P-2017	L	L	L	M

[0287] CYP (Cytochrome P450) enzymes are the major drug metabolizing enzymes present in the liver. The inhibition of CYP enzyme activity (IC_{50}) for each of CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4(BFC) and CYP3A4(BQ) is determined for compounds, where inhibition of metabolism of a known substrate leads to a decrease in the fluorescence of the metabolized product. The fluorescence of the product is monitored as a function of compound concentration.

[0288] Compounds are dissolved in dimethyl sulfoxide to a concentration of 100 mM. These are diluted 1 µL into 82 µL of acetonitrile. An 11 µL aliquot of this solution is then added to 204 µL of cofactor mix (1.3% NADPH Regeneration system Solution A, 1.04% NADPH Regeneration system Solution B from BD Biosciences, 5% acetonitrile and 0.05% dimethyl sulfoxide). These are then serially

diluted 1:1 (160 µL to 160 µL co-factor mix) for a total of 10 points. A 10 µL aliquot of this final mixture is dispensed into 384 well assay plates and incubated for 10 minutes at 37 °C. Enzyme and substrate mix (10 µL; 0.5 pmol CYP1A2/5 µM CEC; 1.0 pmol CYP2C9/75 µM MFC; 0.5 pmol CYP2C19/25 µM CEC; 1.5 pmol CYP2D6/1.5 µM AMMC; 1.0 pmol CYP3A4/50 µM BFC; or 1.0 pmol CYP3A4/40 µM BQ) is added to these assay plates. Assay plates are incubated at 37 °C (CYP1A2-15 min; CYP2C9-45 min; CYP2C19, 2D6 and 3A4-30 min) and read in a Tecan Safire 2 plate reader (CYP1A2, 2C19 and 3A4 409 ex/460 em; CYP2C9 and 2D6 409 ex/530 em). The signal versus compound concentration is used to determine the IC_{50}. The enzymes and substrates for this assay are obtained from BD Biosciences. While other factors are involved in determining CYP effects in vivo, compounds preferably have IC_{50} values of >5 µM, more preferably IC_{50} values of > 10 µM.

[0289] The following table indicates the Cyp inhibition for exemplary compounds according to the invention as indicated:

Compound number	Cyp IC_{50} (µM)					
	1A2	2C19	2C9	2D6	3A4(BFC)	3A4(BQ)
P-1001	> 10	> 10	> 10	> 10	< 5	> 10
P-1002	> 10	> 10	> 10	> 10	> 10	> 10
P-1003	> 10	> 10	5-10	> 10	> 10	5-10
P-1004	> 10	> 10	5-10	> 10	> 10	> 10
P-1005	> 10	5-10	> 10	> 10	5-10	> 10
P-1006	> 10	> 10	5-10	> 10	< 5	> 10
P-1007	> 10	> 10	> 10	> 10	5-10	5-10
P-1008	> 10	> 10	5-10	> 10	> 10	> 10
P-1009	> 10	5-10	< 5	> 10	< 5	> 10
P-1010	> 10	5-10	5-10	> 10	> 10	> 10
P-1011	> 10	5-10	> 10	> 10	< 5	> 10
P-1012	> 10	> 10	> 10	> 10	> 10	> 10
P-1013	> 10	> 10	> 10	> 10	> 10	> 10
P-1014	> 10	> 10	> 10	> 10	> 10	
P-1015	> 10	> 10	> 10	> 10	5-10	
P-1016	> 10	> 10	> 10	> 10	> 10	
P-1020	> 10	> 10	> 10	> 10	> 10	
P-1024	> 10	5-10	> 10	> 10	> 10	
P-1025	> 10	> 10	> 10	> 10	5-10	
P-1026	> 10	> 10	> 10	> 10	> 10	
P-1027	> 10	> 10	> 10	> 10	> 10	
P-1028	> 10	> 10	5-10	> 10	> 10	
P-1029	> 10	5-10	5-10	> 10	> 10	
P-1030	> 10	> 10	> 10	> 10	> 10	
P-1031	> 10	> 10	> 10	> 10	> 10	
P-1032	> 10	5-10	> 10	> 10	> 10	

P-1033	> 10	> 10	> 10	> 10	> 10	
P-1034	> 10	5-10	> 10	> 10	5-10	
P-1035	> 10	5-10	> 10	> 10	5-10	
P-1037	> 10	< 5	> 10	> 10	> 10	
P-1038	> 10	5-10	5-10	> 10	5-10	
P-1039	> 10	> 10	> 10	> 10	5-10	
P-1040	> 10	> 10	> 10	> 10	5-10	> 10
P-1041	> 10	> 10	> 10	> 10	> 10	> 10
P-1042	> 10	5-10	> 10	> 10	> 10	> 10
P-1043	> 10	> 10	> 10	> 10	> 10	> 10
P-1044	> 10	< 5	> 10	> 10	> 10	> 10
P-1045	> 10	< 5	5-10	> 10	5-10	> 10
P-1046	> 10	> 10	> 10	> 10	> 10	> 10
P-1047	> 10	> 10	> 10	> 10	> 10	> 10
P-1048	> 10	> 10	> 10	> 10	> 10	> 10
P-1049	> 10	> 10	> 10	> 10	> 10	> 10
P-1050	> 10	> 10	> 10	> 10	> 10	> 10
P-1051	> 10	> 10	> 10	> 10	> 10	> 10
P-1052	> 10	< 5	< 5	> 10	5-10	> 10
P-1053	> 10	5-10	5-10	> 10	> 10	> 10
P-1054	> 10	> 10	5-10	> 10	> 10	> 10
P-1055	> 10	< 5	5-10	> 10	5-10	> 10
P-1056	> 10	> 10	> 10	> 10	> 10	> 10
P-1057	> 10	> 10	> 10	> 10	> 10	> 10
P-1058	> 10	> 10	> 10	> 10	5-10	> 10
P-1059	> 10	> 10	> 10	> 10	> 10	> 10
P-1060	> 10	> 10	> 10	> 10	> 10	> 10
P-1061	> 10	> 10	> 10	> 10	> 10	> 10
P-1062	> 10	> 10	< 5	> 10	5-10	5-10
P-1063	> 10	5-10	5-10	> 10	5-10	< 5
P-1073	> 10	> 10	> 10	> 10	> 10	> 10
P-1074	> 10	> 10	> 10	> 10	> 10	> 10
P-1077	> 10	> 10	> 10	> 10	> 10	> 10
P-1078	> 10	> 10	< 5	> 10	> 10	5-10
P-1079	> 10	> 10	> 10	> 10	> 10	> 10
P-1081	> 10	> 10	> 10	> 10	> 10	> 10
P-1090	> 10	> 10	> 10	> 10	> 10	> 10
P-1100	> 10	> 10	> 10	> 10	> 10	> 10
P-1101	> 10	> 10	> 10	> 10	> 10	> 10
P-1103	> 10	> 10	> 10	> 10	> 10	> 10
P-1104	> 10	> 10	> 10	> 10	> 10	> 10
P-1107	5-10	> 10	> 10	> 10	> 10	> 10
P-1111	> 10	> 10	5-10	> 10	> 10	> 10
P-1137	> 10	> 10	> 10	> 10	> 10	> 10
P-1139	> 10	> 10	> 10	> 10	> 10	> 10
P-1142	> 10	> 10	> 10	> 10	> 10	> 10
P-1149	> 10	> 10	> 10	> 10	> 10	> 10

P-1150	> 10	> 10	> 10	> 10	> 10	> 10
P-1153	> 10	> 10	> 10	> 10	> 10	> 10
P-1154	> 10	> 10	> 10	> 10	> 10	> 10
P-2001	> 10	5-10	> 10	> 10	> 10	> 10
P-2002	> 10	< 5	< 5	> 10	5-10	5-10
P-2003	> 10	> 10	< 5	> 10	5-10	5-10
P-2004	> 10	> 10	< 5	> 10	> 10	> 10
P-2005	> 10	> 10	< 5	> 10	> 10	> 10
P-2006	> 10	< 5	< 5	> 10	5-10	> 10
P-2007	> 10	> 10	< 5	> 10	> 10	> 10
P-2008	> 10	5-10	5-10	> 10	> 10	> 10
P-2009	> 10	> 10	> 10	> 10	> 10	> 10
P-2010	> 10	> 10	5-10	< 5	> 10	> 10
P-2011	> 10	< 5	> 10	5-10	> 10	> 10
P-2012	> 10	> 10	> 10	> 10	> 10	> 10
P-2013	> 10	> 10	> 10	> 10	5-10	> 10
P-2015	> 10	> 10	> 10	> 10	> 10	> 10

[0290] 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.

Example 10: Efficacy of Compounds in Combination with Standard-of-Care Chemotherapeutic agents in four human cancer cell lines.

[0291] Compounds of the invention, such as compounds of Formula I, in combination with a standard chemotherapeutic agent, such as 5-fluorouracil, carboplatin, dacarbazine, gefitinib, oxaliplatin, paclitaxel, SN-38, temozolomide, or vinblastine, can be assessed for their effectiveness in killing human tumor cells. Such assays are known in the art, for example, as described in US Patent Application Serial number 11/473,347, the disclosure of which is hereby incorporated by reference as it relates to such assays.

[0292] Additional features of the complex can be used to demonstrate improved properties, such as comparison of the intrinsic dissolution rate of a similarly prepared substantially amorphous citrate complex or formulation thereof as compared to that of a crystalline form of the compound or similar formulation thereof in simulated gastric fluid (SGF) without enzyme and in simulated intestinal fluid (SIF). A pellet of test sample is dissolved in the appropriate fluid, and the UV absorbance as a function of time is measured at 254 nm (SGF) or 310 nm (SIF) and plotted.

[0293] All patents 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.

[0294] 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.

[0295] The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. Thus, for an embodiment of the invention using one of the terms, the invention also includes another embodiment wherein one of these terms is replaced with another of these terms. In each embodiment, the terms have their established meaning. Thus, for example, one embodiment may encompass a method "comprising" a series of steps,

another embodiment would encompass a method "consisting essentially of" the same steps, and a third embodiment would encompass a method "consisting of" the same steps. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

[0296] 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.

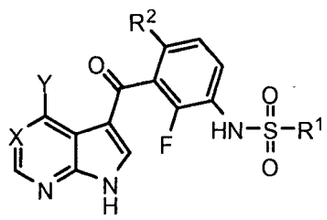
[0297] Also, unless indicated to the contrary, where various numerical values are provided for embodiments, additional embodiments are described by taking any 2 different values as the endpoints of a range. Such ranges are also within the scope of the described invention.

[0298] Thus, additional embodiments are within the scope of the invention and within the following claims.

CLAIMS

What is claimed is:

1. A compound having the chemical structure of Formula I,



Formula I

or a pharmaceutically acceptable salt, hydrate or solvate thereof,

wherein:

X is –N= or –C(R^5)=;

Y is selected from the group consisting of fluoro, chloro, bromo, iodo, lower alkyl, lower alkoxy, haloalkyl, CN, -OH, cycloalkyl, -OR^8, and –N(R^3)(R^4); wherein:

R^3 is hydrogen and R^4 is selected from the group consisting of (i) hydrogen, -OR^8 and lower alkyl optionally substituted with one or more R^{11}; (ii) cycloalkyl or cycloalkylalkyl, each of which is optionally substituted with one or more R^{12}; (iii) heterocycloalkyl or heterocycloalkylalkyl, each of which is optionally substituted with one or more R^{13}; (iv) aryl or arylalkyl, each of which is optionally substituted with one or more R^{14}, optionally, wherein the two adjacent R^{14} groups on the aryl ring are taken together to form a 5 or 6-membered hetero cyclic aromatic ring having from 1-4 heteroatoms selected from O or N; and (v) heteroaryl or heteroarylalkyl, each of which is optionally substituted with one or more R^{15}; or

R^3 and R^4 are both lower alkyl; or

R^3 and R^4 combine with the nitrogen atom to which they are attached to form a 3-7 membered ring having 0-1 additional ring heteroatom selected from O, N or S, wherein the nitrogen or sulfur atom is optionally oxidized;

R^1 is selected from the group consisting of lower alkyl, haloalkyl, haloalkoxy, fluoro substituted lower alkyl, cycloalkyl optionally substituted with one or more R^7, heterocycloalkyl, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, aryl optionally substituted with one or more R^6 and heteroaryl optionally substituted with one or more R^7;

R^2 is hydrogen, fluoro, chloro, or lower alkyl optionally substituted with one or more fluorine;

R^5 is selected from the group consisting of hydrogen, fluoro, chloro, -CN, lower alkyl optionally substituted with one or more R^{16}, and lower alkoxy optionally substituted with one or more R^{17};

each R^6, when present, is independently selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, $-C(O)-O-R^{15}$, $-N(H)-C(O)-R^{16}$, and heteroaryl optionally substituted with one or more lower alkyl; or two R^5 on adjacent carbons combine to form a fused heterocycloalkyl optionally substituted with one or more lower alkyl;

each R^7, when present, is independently selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, lower alkoxy, $-C(O)-O-R^{20}$, and heteroaryl optionally substituted with one or more lower alkyl;

R^8 is hydrogen, lower alkyl optionally substituted with one or more fluorine, or, when R^8 is a C_{2-6} alkyl, said alkyl may optionally be substituted with one or more R^{21}; cycloalkyl optionally substituted with one or more R^{21}, or heterocycloalkyl optionally substituted with one or more R^{21};

each R^{11}, when present, is independently selected from the group consisting of fluoro, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, cycloalkyl optionally substituted with one or more R^{12}, heterocycloalkyl optionally substituted with one or more R^{13}, aryl optionally substituted with one or more R^{14}, and heteroaryl optionally substituted with one or more R^{15};

each R^{12}, when present, is independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, $-N(H)-C(O)-R^{22}$, $-N(H)-S(O)_2-R^{23}$, $C(O)-R^{24}$, and $S(O)_2-R^{25}$;

each R^{13}, when present, is independently selected from the group consisting of fluoro, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, $-N(H)-C(O)-R^{26}$, $-N(H)-S(O)_2-R^{27}$, $C(O)-R^{28}$, $S(O)_2-R^{29}$, and lower alkyl optionally substituted with one or more R^{30};

each R^{14} and R^{15}, when present, are independently selected from the group consisting of fluoro, chloro, -OH, $-NH_2$, -CN, $-NO_2$, $-N(H)-C(O)-R^{31}$, $-N(H)-S(O)_2-R^{32}$, $C(O)-R^{33}$, $S(O)_2-R^{34}$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, aryl optionally substituted with one or more R^{35}, and heteroaryl optionally substituted with one or more R^{36};

each R^{16}, when present, is independently fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{17}, when present, is independently fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{18} and R^{20}, when present, are independently hydrogen, lower alkyl or fluoro substituted lower alkyl;

each R^{19}, R^{22}, R^{23}, R^{26}, R^{27}, R^{31} and R^{32}, when present, are independently lower alkyl or fluoro substituted lower alkyl;

each R^{21}, when present, is fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{24}, R^{25}, R^{28}, R^{29}, R^{33}, and R^{34}, when present, are independently lower alkyl, fluoro substuted lower alkyl, -OH, lower alkoxy, fluor substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{30}, when present, is independently fluoro, aryl optionally substituted with one or more R^{35} or heteroaryl optionally substituted with one or more R^{36}; and

each R^{35} and R^{36}, when present, are independently selected from the group consisting of fluoro, chloro, -OH, $-NH_2$, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino.

2. The compound of claim **1**, wherein:

X is –N= or $-C(R^5)=$, wherein R^5 is selected from the group consisting of hydrogen, fluoro, chloro, -CN, lower alkyl and lower alkoxy, wherein the lower alkyl or lower alkoxy is optionally substituted with from one or three groups selected from fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

Y is selected from the group consisting of fluoro, chloro, bromo, iodo, lower alkyl, lower alkoxy, haloalkyl, CN, -OH, cycloalkyl, $-OR^8$, and $-N(R^3)(R^4)$; wherein:

R^3 is hydrogen and R^4 is selected from the group consisting of (i) hydrogen, $-OR^8$ and lower alkyl optionally substituted with from one to three R^{11}; (ii) cycloalkyl or cycloalkylalkyl, each of which is optionally substituted with from one to three R^{12}; (iii) heterocycloalkyl or heterocycloalkylalkyl, each of which is optionally substituted with from one to three R^{13}; (iv) aryl or arylalkyl, each of which is optionally substituted with from one to three R^{14} optionally, wherein the two adjacent R^{14} groups on the aryl ring are taken together to form a 5 or 6-membered heterocyclic aromatic ring having from 1-4 heteroatoms selected from O or N; and (v) heteroaryl or heteroarylalkyl, each of which is optionally substituted with from one to three R^{15}; or

R^3 and R^4 are both lower alkyl; or

R^3 and R^4 are combined with the nitrogen atom to which they are attached to form a three to seven membered ring having 0-1 additional ring heteroatom selected from O, N or S, wherein the nitrogen or sulfur atom is optionally oxidized;

R^1 is selected from the group consisting of lower alkyl, haloalkyl, haloalkoxy, fluoro substituted lower alkyl, cycloalkyl optionally substituted with from one to three R^7, heterocycloalkyl, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, aryl optionally substituted with from one to three R^6 and heteroaryl optionally substituted with one to three R^7;

R^2 is hydrogen, fluoro, chloro, or lower alkyl optionally substituted with from one to five fluorine atoms;

each R^6, when present, is independently selected from the group consisting of fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, $-C(O)-O-R^{15}$, $-N(H)-C(O)-R^{16}$, and heteroaryl optionally substituted with one or more lower alkyl; or two R^5 on adjacent carbons combine to form a fused heterocycloalkyl optionally substituted with one or more lower alkyl;

each R^7, when present, is independently selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, lower alkoxy, $-C(O)-O-R^{20}$, and heteroaryl optionally substituted with one or more lower alkyl;

R^8 is hydrogen, lower alkyl optionally substituted with one or more fluorine, or, when R^8 is a C_{2-6} alkyl, said alkyl may optionally be substituted with one or more R^{21}; cycloalkyl optionally substituted with one or more R^{21}, or heterocycloalkyl optionally substituted with one or more R^{21};

each R^{11}, when present, is independently selected from the group consisting of fluoro, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, cycloalkyl optionally substituted with one or more R^{12}, heterocycloalkyl optionally substituted with one or more R^{13}, aryl optionally substituted with one or more R^{14}, and heteroaryl optionally substituted with one or more R^{15};

each R^{12}, when present, is independently selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, $-N(H)-C(O)-R^{22}$, $-N(H)-S(O)_2-R^{23}$, $C(O)-R^{24}$, and $S(O)_2-R^{25}$;

each R^{13}, when present, is independently selected from the group consisting of fluoro, -OH, lower alkoxy, fluoro substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, $-N(H)-C(O)-R^{26}$, $-N(H)-S(O)_2-R^{27}$, $C(O)-R^{28}$, $S(O)_2-R^{29}$, and lower alkyl optionally substituted with one or more R^{30};

each R^{14} and R^{15}, when present, are independently selected from the group consisting of fluoro, chloro, -OH, $-NH_2$, -CN, $-NO_2$, $-N(H)-C(O)-R^{31}$, $-N(H)-S(O)_2-R^{32}$, $C(O)-R^{33}$, $S(O)_2-R^{34}$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, aryl optionally substituted with one to three R^{35}, and heteroaryl optionally substituted with one to three R^{36};

each R^{18} and R^{20}, when present, are independently hydrogen, lower alkyl or fluoro substituted lower alkyl;

each R^{19}, R^{22}, R^{23}, R^{26}, R^{27}, R^{31} and R^{32}, when present, are independently lower alkyl or fluoro substituted lower alkyl;

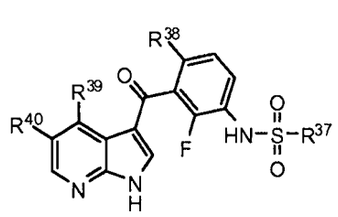
each R^{21}, when present, is fluoro, -OH, lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{24}, R^{25}, R^{28}, R^{29}, R^{33}, and R^{34}, when present, are independently lower alkyl, fluoro substuted lower alkyl, -OH, lower alkoxy, fluor substituted lower alkoxy, $-NH_2$, mono-alkylamino, di-alkylamino, cycloalkylamino, or heterocycloalkylamino;

each R^{30}, when present, is independently fluoro, aryl optionally substituted with one or more R^{35} or heteroaryl optionally substituted with one to three R^{36}; and

each R^{35} and R^{36}, when present, are independently selected from the group consisting of fluoro, chloro, -OH, $-NH_2$, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino.

3. The compound of claim **1** or **2**, having Formula II:



II

wherein:

R^{37} is selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, cycloalkyl, mono-alkylamino, di-alkylamino, cycloalkylamino, heterocycloalkylamino, phenyl optionally substituted with one or more R^{41} and heteroaryl optionally substituted with one or more R^{42};

R^{38} is hydrogen, fluoro, chloro, or lower alkyl optionally substituted with one or more fluorine;

R^{39} and R^{40} are each independently selected from the group consisting of fluoro, chloro, -CN, -OH, $-NH_2$, lower alkoxy, lower alkyl optionally substituted with one or more R^{43}, lower alkenyl optionally substituted with C(O)-O-R^{44}, lower alkynyl optionally substituted with lower alkyl optionally substituted with one or more fluorine, or, on a non-alkynyl carbon thereof, R^{45}, lower alkoxy optionally substituted with R^{46}, mono-alkylamino, di-alkylamino, cycloalkylamino, cycloalkylalkyl-NH-, heterocycloalkylamino and heterocycloalkylalkyl-NH-;

each R^{41}, when present, is independently selected from the group consisting of halogen, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, -C(O)-O-R^{47}, -N(H)-C(O)-R^{48}, and heteroaryl optionally substituted with one or more lower alkyl; or two R^{41} on adjacent carbons combine to form a fused heterocycloalkyl optionally substituted with one or more lower alkyl;

each R^{42}, when present, is independently selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, -C(O)-O-R^{49}, and heteroaryl optionally substituted with one or more lower alkyl;

each R^{43}, when present, is independently selected from the group consisting of fluoro, -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino;

each R^{44}, when present, is independently hydrogen or lower alkyl optionally substituted with one or more fluorine;

each R^{45}, when present, is independently selected from the group consisting of -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino;

each R^{46}, when present, is independently selected from the group consisting of -OH, lower alkoxy, mono-alkylamino, di-alkylamino, cycloalkylamino, and heterocycloalkylamino;

each R^{47}, when present, is independently hydrogen or lower alkyl optionally substituted with one or more fluorine;

each R^{48}, when present, is independently lower alkyl optionally substituted with one or more fluorine; and

each R^{49}, when present, is independently hydrogen or lower alkyl optionally substituted with one or more fluorine.

4. The compound of claim **3**, wherein R^{37} is lower alkyl, fluoro substituted lower alkyl or phenyl, optionally substituted with from 1-3 R^{41} groups.

5. The compound of claim **4**, wherein R^{37} is lower alkyl, fluoro substituted lower alkyl or phenyl substituted with from 1-3 groups selected from fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, -C(O)-O-R^{47} or -N(H)-C(O)-R^{48}.

6. The compound of claim **5**, wherein R^{37} is lower alkyl or phenyl substituted with from 1-2 groups selected from fluoro, chloro, -CN, $-NO_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy or fluoro substituted lower alkoxy.

7. The compound of claim **3**, wherein R^{38} is H, -F or fluoro substituted lower alkyl.

8. The compound of claim **3**, wherein R^{39} is fluoro, chloro, -CN, -OH, $-NH_2$, lower alkoxy, lower alkyl optionally substituted with one or more R^{43}, cycloalkylamino, cycloalkylalkyl-NH-, heterocycloalkylamino and heterocycloalkylalkyl-NH-.

9. The compound of claim **3**, wherein R^{40} is H, lower alkyl optionally substituted with one or more R^{43}, halogen, lower alkoxy or –CN.

10. The compound of any of claims **3-9,** wherein R^{37} is lower alkyl or phenyl optionally substituted with 1-2 members selected from CF_3 or halogen.

11. The compound of claim **10**, wherein R^{37} is propyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl or 2,5-difluoro-substituted phenyl.

12. The compound of claim **11**, wherein R^{37} is propyl, 4-trifluoromethylphenyl, 2-fluorophenyl, 3-fluorophenyl or 2,5-difluoro-substituted phenyl.

13. The compound of any of claims **3-9,** wherein R^{38} is H, F or CF_3.

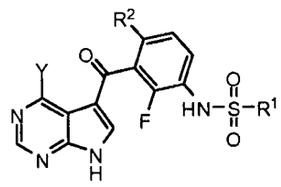
14. The compound of any of claims **3-9**, wherein R^{38} is F.

15. The compound of any of claims **3-9,** wherein R^{39} is fluoro, chloro, -CN, -OH, $-NH_2$, lower alkyl optionally substituted with fluoro, lower alkoxy, cycloalkylamino, cycloalkylalkyl-NH-, heterocycloalkylamino and heterocycloalkylalkyl-NH-.

16. The compound of claim **15**, wherein R^{39} is fluoro, chloro, -CN, -OH, $-NH_2$, CH_3, CH_3O-, CF_3, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl,

cyclopentylmethyl, cyclohexylmethyl, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cyclopropylmethylamino, cyclobutylmethylamino, cyclopentylmethylamino, cyclohexylmethylamino, 2-tetrahydrofuranylamino, 3-tetrahydrofuranylamino or 4-tetrahydropyranylamino.

17. The compound of claim **1** or **2**, having Formula III:



III

18. The compound of any of claims **1**, **2** or **17**, wherein X is selected from the group consisting of –N=, –CH=, -C(CH_3)=, -C(OCH_3)=, -C(F)=, -C(CN)=, -C(CH_2OH)= and –C(Cl)=.

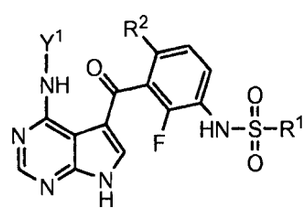
19. The compound of any of claims **1**, **2** or **17**, wherein X is –N=, –CH=, -C(CH_3)=, -C(F)= or -C(CN)=.

20. The compound of any of claims **1**, **2** or **17**, wherein X is –N=.

21. The compound of any of claims **1**, **2** or **17**, wherein Y is fluoro, chloro, bromo, iodo, lower alkyl, lower alkoxy, haloalkyl, CN, -OH, cycloalkyl, -OR^8 or –NH(R^4).

22. The compound of any of claims **1**, **2** or **17**, wherein Y is CH_3, ethyl, methoxy, ethyoxy, isobutyl, CN, OH, F, Cl, Br, I, NH_2, butyoxy, 2-methylpropoxy, 4-tetrahydropyranyloxy, 2-tetrahyrofuranyloxy, 3-tetrahyrofuranyloxy, alkoxyamino or HO-NH-.

23. The compound of claims **1** or **2**, having Formula IIIa:



IIIa

wherein Y^1 is lower alkyl optionally substituted with from one to three R^{11}, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, wherein:

(v) the cycloalkyl and cycloalkylalkyl are each optionally substituted with from one to three R^{12};

(vi) the heterocycloalkyl and heterocycloalkylalkyl are each optionally substituted with from one to three R^{13};

(vii) the aryl and arylalkyl are each optionally substituted with from one to three R^{14} optionally, wherein the two adjacent R^{14} groups on the aryl ring are taken together to form a 5 or 6-membered hetero aromatic ring having from 1-4 heteroatoms selected from O or N; and

(viii) the heteroaryl and heteroarylalkyl are each optionally substituted with from one to three R^{15}.

24. The compound of claim **23**, wherein Y^1 is selected from lower alkyl, halogen substituted lower alkyl, 2-hydroxyethyl, cyclopropylamino, cyclobutyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexyl, 2-oxetanyl, 2-oxetanylmethyl, 3-oxetanyl, 3-oxetanylmethyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, 2-tetrahydrofuranylmethyl, 3-tetrahydrofuranylmethyl, 2-tetrahydropyranylmethyl, 3-tetrahydropyranylmethyl, 4-tetrahydropyranylmethyl, 1-methyl-2-aziridinyl, 1-methyl-2-aziridinylmethyl, 1-methyl-2-azetidinyl, 1-methyl-2-azetidinylmethyl, 1-methyl-3-azetidinyl, 1-methyl-3-azetidinylmethyl, 1-methyl-2-pyrrolidinyl, 1-methyl-2-pyrrolidinylmethyl, 1-methyl-3-pyrrolidinyl, 1-methyl-3-pyrrolidinylmethyl, 1-methyl-2-piperidinyl, 1-methyl-2-piperidinylmethyl, 1-methyl-3-piperidinyl, 1-methyl-3-piperidinylmethyl, 1-methyl-4-piperidinyl, 1-methyl-4-piperidinylmethyl, 1-methylsulfonyl-2-piperidinyl, 1-methylsulfonyl-2-piperidinylmethyl, 1-methylsulfonyl-3-piperidinyl, 1-methylsulfonyl-3-piperidinylmethyl, 1-methylsulfonyl-4-piperidinyl, 1-methylsulfonyl-4-piperidinylmethyl, 1,1-dioxo-4-thianyl, 1,1-dioxo-4-thianylmethyl, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-benzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-pyridyl, 2-pyridylmethyl, 3-pyridyl, 3-pyridylmethyl, 4-pyridyl, 4-pyridylmethyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-dimethylaminophenyl, 3-dimethylaminophenyl, 4-dimethylaminophenyl, 2-dimethylaminobenzyl, 2-dimethylaminobenzyl, 3-dimethylaminobenzyl, 4-dimethylaminobenzyl, 2-hydoxyphenyl, 3-hydoxyphenyl, 4-hydoxyphenyl, 2-hydroxybenzyl, 3-hydroxybenzyl, 4-hydroxybenzyl, 2-carboxyphenyl, 3-carboxyphenyl, 4-carboxyphenyl, 2-carboxybenzyl, 3-carboxybenzyl, 4-carboxybenzyl, 2-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methoxycarbonylphenyl, 2-methoxycarbonylbenzyl, 3-methoxycarbonylbenzyl, 4-methoxycarbonylbenzyl, 1-alkyl-4-pyrazolyl, 1-alkyl-4-pyrazolylmethyl, 3-

pyridazinyl, pyridazinylmethyl, 4-pyridazinyl, 4-pyridazinylmethyl, triazolyl, triazolymethyl, tetrazolyl, tetrazolymethyl, 2,1,3,-benzoxadiazolyl, 2,1,3-benzoxadiazol-5-yl, 2,1,3,-benzoxadiazolyl-methyl, 2,1,3-benzoxadiazol-5ylmethyl, 2,1,3,-benzothiadiazolyl, 2,1,3-benzothiadiazol-5-yl, 2,1,3,-benzothiadiazolyl-methyl, 2,1,3-benzothiadiazol-5ylmethyl, 1H-1,2,4-triazol-5-yl, 1H-1,2,4-triazol-5-methyl, 2-oxobenzimidazol-4-yl, 2-oxobenzimidazol-4-methyl, 2-oxobenzimidazol-5-yl, 2-oxobenzimidazol-5-methyl, 1,1,-dioxo-thiolan-3-yl, 1,1-dioxothiolan-3-methyl, 3-(2-methyl-1,2,3,4-tetrazol-5-yl)phenyl, 3-(2-methyl-1,2,3,4-tetrazol-5-yl)benzyl, 3-(5-methyl-1,2,3,4-tetrazol-1-yl)phenyl, 3-(1,2,4-triazol-5-yl)phenyl, 3-(1,2,,4-triazol-5-yl)benzyl, 3-3-methyl-4H-1,2,4-triazol-5-methyl or 2-(3-methyl-4H-1,2,4-triazol-5-yl)ethyl.

25. The compound of any of claims **17-23** or **24**, wherein R^2 is H or F.

26. The compound of any of claims **17-23** or **24**, wherein R^1 is lower alkyl, cycloalkyl optionally substituted with 1-2 groups selected from halogen or lower alkyl, heterocycloalkyl, heteroaryl optionally substituted with lower alkyl or lower alkoxy, phenyl optionally subtitued with 1-2 substitutents selected from lower alkyl, halogen, lower alkoxy, haloalkyl, haloalkoxy or CN.

27. The compound of claim **26**, wherein R^1 is methyl, propyl, isobutyl, 2-methylpropyl, CF_3, CF_3CH_2-, CHF_2CH_2-, 4-trifluorophenyl, 2-trifluorophenyl, 3-trifluorophenyl, 3,5-dimethylphenyl, 4-propylphenyl, 3-fluoro-4-methoxyphenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-fluoro-3-methoxyphenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,4-difluorophenyl, 2-pyridyl, 3-pyridyl, 5-methoxy-2-pyridyl, 3-methoxy-2-pyridyl, 4-methoxy-2-pyridyl, 6-methyl-2-pyridyl, 5-methyl-2-pyridyl, 4-methyl-2-pyridyl, 3-methyl-2-pyridyl, dialkylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, cycloprpyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-difluorocyclohexyl, 1-methyl-4-pyrazolyl, 1-ethyl-4-pyrazolyl, 1-methyl-3-pyrazolyl, 1-ethyl-3-pyrazolyl, 6-methyl-3-pyridyl, 5-methyl-3-pyridyl, 4-methyl-3-pyridyl or 2-methyl-3-pyridyl.

28. The compound of claim **27**, wherein R^1 is 2-fluorophenyl, 3-fluorophenyl, 2,5-difluorophenyl or 4-lower alkyl-substituted phenyl, wherein lower alkyl is optionally substituted with one or more fluorine.

29. The compound of any of claims **17-22**, wherein Y is $-NR^3R^4$, wherein R^3 and R^4 are combined with the nitrogen atom to which they are attached to form a three to seven membered ring having 0-1 additional heteroatom selected from O, N or S, wherein the nitrogen and sulfur atoms are optionally oxidized.

30. The compound of claim **29**, wherein Y is 1-aziridinyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl or 1-azepanyl.

31. A compound selected from the group consisting of:
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1001**),
Propane-1-sulfonic acid [3-(4-ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1002**),
2-Methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1003**),
2-Methyl-propane-1-sulfonic acid [2,4-difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1004**),
N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1005**),
N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1006**),
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1007**),
N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide (**P-1008**),
N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1009**),
N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1010**),
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1012**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1014**),
N-[2,4-Difluoro-3-(4-isobutyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1015**),
N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1016**),
6-Methoxy-pyridine-3-sulfonic acid [2,4-difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1018**),

N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-ethyl-benzenesulfonamide (**P-1019**),

N-{2,4-Difluoro-3-[4-(tetrahydro-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1021**),

Propane-1-sulfonic acid [2,4-difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-amide (**P-1022**),

N-[3-(4-Cyano-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1023**),

N-[2,4-Difluoro-3-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3,5-dimethyl-benzenesulfonamide (**P-1025**),

N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3,5-dimethyl-benzenesulfonamide (**P-1027**),

N-[2,4-Difluoro-3-(4-isobutoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1028**),

N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1029**),

N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-4-propyl-benzenesulfonamide (**P-1030**),

Propane-1-sulfonic acid [3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1033**),

N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1034**),

N-[2,4-Difluoro-3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-3-fluoro-4-methoxy-benzenesulfonamide (**P-1036**),

N-[3-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-1038**),

N-[3-(4-Cyclopropylmethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1053**),

N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2-fluoro-benzenesulfonamide (**P-1070**),

N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1071**),

N-[3-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-

benzenesulfonamide (**P-1107**),
N-[3-(4-Cyclopropylmethoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1181**),
N-[2,4-Difluoro-3-(4-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1182**),
N-[2,4-Difluoro-3-(4-hydroxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1183**),
N-[3-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-2,4-difluoro-phenyl]-2,5-difluoro-benzenesulfonamide (**P-1184**),
Propane-1-sulfonic acid [2,4-difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-2015**),
N-[2,4-Difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-2016**),
N-[2,4-Difluoro-3-(4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide (**P-2017**), and
any pharmaceutically acceptable salt thereof.

32. A composition comprising a compound of any of claims **1-31** and a pharmaceutically acceptable excipient or carrier.

33. A pharmaceutical composition comprising a compound of any of claims **1-31** and another drug.

34. A kit comprising a compound according to any of claims **1-31** or a composition according to Claim **32** or **33**.

35. A method for treating a Raf protein kinase mediated disease or condition in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of claims **1-31** or a composition of claims **32** or **33**.

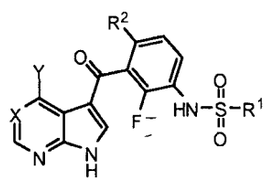
36. A method for treating a Raf protein kinase mediated disease or condition in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound according to any one of claims **1-31** and another drug or a pharmaceutically acceptable salt thereof.

37. The method of claim **35** or **36**, wherein the disease or condition is selected from the group consisting of 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 mycloid 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).

38. The method of claim **37** wherein 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, testicular cancer, and cholangiocarcinoma.

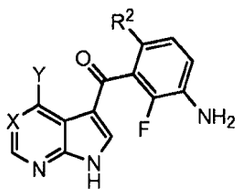
39. A method for preparing a compound of Formula I according to claim **1**



I

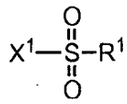
said method comprising:

contacting a compound of Formula IVc:



IVc

with a compound of Formula V:



V

under conditions sufficient to form the compound of Formula I, wherein:

X^1 is a halogen.

40. The method of claim **39**, wherein X is –N=, –CH=, -C(CH_3)=, -C(OCH_3)=, -C(F)=, -C(CN)=, -C(CH_2OH)= or –C(Cl)=.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/57293

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/90; A61K 31/519 (2010.01)
USPC - 514/265.1
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)
USPC: 514/265.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/256, 258.1, 427 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Database Searched: PUBWEST (PGPUB, EPAB, JPAB, USPT). Search Terms Used pyrimidine$ near4 $pyrrolo, $benzene sulfonamide, trifluoromethylbenzene sulfonamide, benzenesulfonamide, head injury, spinal cord injury, acute pain, chronic pain, cancer-related pain, migraine, atherosclerosis, reperfusion injury, psoriasis, eczema, arthritis, aut

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2008/0167338 A1 (Spevak et al.) 10 July 2008 (10.07.2008) entire document especially para [0009]-[0012]	1-9, 17, 23-24, 31, 39-40
Y	US 5,958,930 A (Gangjee) 28 September 1999 (28.9.1999) especially figure 1 and 2	1-9, 17, 23-24, 31, 39-40
Y	US 2009/0076046 A1 (Zhang et al.) 19 March 2009 (19.03.2009) especially para [1140], scheme 21	39-40
P/X	US 2009/0286783 A1 (Ibrahim et al.) 19 November 2009 (19.11.2009) entire document	1-9, 17, 23-24, 31

☐ 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
09 January 2011 (09.01.2011)	25 JAN 2011
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: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/57293

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.: 10-16, 18-22, 25-30 and 32-38
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 CINASAS, E INDICACIONES PARA ELLO

CAMPO DE LA INVENCIÓN

[0001] Se dan a conocer compuestos novedosos y usos de los mismos. En ciertas modalidades los compuestos dados a conocer son inhibidores de cinasas.

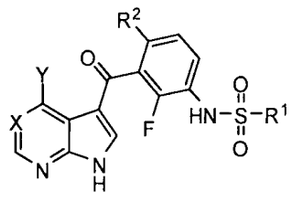
SUMARIO DE LA INVENCIÓN

[0002] En ciertos aspectos y modalidades dados a conocer en este documento, se proporcionan compuestos, así como diversas sales de los mismos, formulaciones de los mismos, conjugados de los mismos, derivados de los mismos, formas de los mismos y usos de los mismos. En algunas modalidades, los compuestos son de la Fórmula I, Fórmula II, Fórmula II y Fórmula IIIa, como se describe a continuación. En ciertas modalidades, los compuestos inhiben una o más proteína cinasas Raf, incluyendo una o más de A-Raf, B-Raf, y c-Raf-1, y cualquier mutación de las mismas. En ciertas modalidades, los compuestos inhiben a proteína cinasa c-Raf-1. En ciertas modalidades, los compuestos inhiben a proteína cinasa c-Raf-1 de manera selectiva a otras proteína cinasas Raf. En ciertas modalidades, los compuestos inhiben una proteína cinasa mutante B-Raf V600X (donde X es un aminoácido diferente a valina, por ejemplo, alanina, arginina, ácido aspártico, glicina, lisina o metionina). En ciertas modalidades, los compuestos inhiben una proteína cinasa mutante B-Raf V600E. En ciertas modalidades, los compuestos inhiben una proteína cinasa mutante B-Raf V600E de manera selectiva en relación con otras proteína cinasas Raf, incluyendo a proteína cinasa B-Raf. En ciertas modalidades, los compuestos inhiben cada una de las proteína cinasas c-Raf-1, B-Raf, B-Raf V600X, y B-Raf V600E.

[0003] También, de acuerdo con la presente invención, se contemplan métodos para el uso de los compuestos para tratar enfermedades y padecimientos asociados con la regulación de la actividad de una o más de las proteína cinasas Raf, incluyendo una o más de A-Raf, B-Raf, y c-Raf-1, y cualquier mutación de las mismas. De esta manera, se proporciona el uso de compuestos para métodos terapéuticos que implican la modulación de proteína cinasas. En ciertas modalidades, los compuestos inhiben la actividad en una o más de las cinasas Raf, incluyendo A-Raf, B-Raf y/o c-Raf-1, incluyendo cualquier mutación de las mismas. En ciertas modalidades, los compuestos se utilizan para métodos terapéuticos que implican la modulación de una o más de las proteína cinasas Raf, incluyendo el tratamiento de una diversidad de indicaciones, incluyendo, pero sin limitarse a, melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, cáncer colorrectal, cáncer de tiroides, cáncer pulmonar, cáncer ovárico, cáncer de próstata, cáncer hepático, cáncer de vesícula biliar, tumores de estroma gastrointestinal, cáncer del tracto biliar, colangiocarcinoma, dolor agudo, dolor crónico y enfermedad renal poliquística. En ciertas modalidades, los compuestos se utilizan para métodos terapéuticos que implican la modulación de la proteína cinasa mutante Raf V600E, incluyendo el tratamiento de una diversidad de indicaciones, incluyendo, pero sin limitarse a, melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico,

cáncer colorrectal, cáncer de tiroides, cáncer pulmonar, cáncer ovárico, cáncer de próstata, cáncer hepático, cáncer de vesícula biliar, tumores de estroma gastrointestinal, cáncer del tracto biliar, y colangiocarcinoma. En ciertas modalidades, los compuestos se utilizan para métodos terapéuticos que implican la modulación de la proteína cinasa c-Raf-1, incluyendo el tratamiento de una diversidad de indicaciones, incluyendo, pero sin limitarse a, dolor agudo, dolor crónico y enfermedad renal poliquística.

[0004] En un primer aspecto, se proporcionan compuestos que tienen la estructura de acuerdo con la siguiente Fórmula I:



Fórmula I

o una sal farmacéuticamente aceptable de los mismos,

en donde:

X es –N= o –C(R^5)=;

Y se selecciona del grupo que consiste en flúor, cloro, bromo, yodo, alquilo inferior, alcoxi inferior, haloalquilo, CN, -OH, alquilo sustituido con flúor, cicloalquilo, -OR^8, y –N(R^3)-R^4;

R^1 se selecciona del grupo que consiste en alquilo inferior, haloalquilo, haloalcoxi, alquilo inferior sustituido con flúor, cicloalquilo opcionalmente sustituido con uno o más R^7, heterocicloalquilo, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, arilo opcionalmente sustituido con uno o más R^6 (por ejemplo, R^1 es fenilo 2-fluoro-sustituido, fenilo 3-fluoro-sustituido, fenilo 2,5-difluoro-sustituido o fenilo 4-alquilo inferior-sustituido, en donde el alquilo inferior se sustituye opcionalmente con uno o más flúor), y heteroarilo opcionalmente sustituido con uno o más R^7;

R^2 es hidrógeno, flúor, cloro o alquilo inferior opcionalmente sustituido con uno o más flúor;

R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en hidrógeno, -OR^8, alquilo inferior opcionalmente sustituido con uno o más R^{11}, cicloalquilo opcionalmente sustituido con uno o más R^{12}, cicloalquilalquilo opcionalmente sustituido con uno o más R^{12}, heterocicloalquilo opcionalmente sustituido con uno o más R^{13}, heterocicloalquilalquilo opcionalmente sustituido con uno o más R^{13}, arilo opcionalmente sustituido con uno o más R^{14}, arilalquilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo opcionalmente sustituido con uno o más R^{15};

o R^3 y R^4 son alquilo inferior;

o R^3 y R^4 se combinan con el nitrógeno al cual se unen para formar cicloalquilamino o R^3 y R^4 se combinan con el átomo de nitrógeno al cual se unen para formar un anillo de 3-7 miembros que tiene 0-1 heteroátomos adicionales seleccionados de O o N;

R^5 se selecciona del grupo que consiste en hidrógeno, flúor, cloro, -CN, alquilo inferior opcionalmente sustituido con uno o más R^{16}, y alcoxi inferior opcionalmente sustituido con uno o más R^{17};

cada R^6, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, cloro, -CN, -NO_2, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior

sustituido con flúor, -C(O)-O-R^{18}, -N(H)-C(O)-R^{19}, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior; o dos R^6 en carbonos adyacentes se combinan para formar un heterocicloalquilo fusionado opcionalmente sustituido con uno o más alquilo inferior;

cada R^7, cuando se presenta, se selecciona independientemente del grupo que consiste en alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, -C(O)-O-R^{20}, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior;

R^8 es hidrógeno, alquilo inferior opcionalmente sustituido con uno o más flúor, o, cuando R^8 es un alquilo C_{2-6}, el alquilo opcionalmente puede sustituirse con uno o más R^{21}; cicloalquilo opcionalmente sustituido con uno o más R^{21}, o heterocicloalquilo opcionalmente sustituido con uno o más R^{21};

cada R^{11}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, cicloalquilo opcionalmente sustituido con uno o más R^{12}, heterocicloalquilo opcionalmente sustituido con uno o más R^{13}, arilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo opcionalmente sustituido con uno o más R^{15};

cada R^{12}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, -N(H)-C(O)-R^{22}, -N(H)-$S(O)_2$-R^{23}, C(O)-R^{24}, y $S(O)_2$-R^{25};

cada R^{13}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, -N(H)-C(O)-R^{26}, -N(H)-$S(O)_2$-R^{27}, C(O)-R^{28}, $S(O)_2$-R^{29}, y alquilo inferior opcionalmente sustituido con uno o más R^{30};

cada R^{14} y R^{15}, cuando se presenta, se seleccionan independientemente del grupo que consiste en flúor, cloro, -OH, -NH_2, -CN, -NO_2, -N(H)-C(O)-R^{31}, -N(H)-$S(O)_2$-R^{32}, C(O)-R^{33}, $S(O)_2$-R^{34}, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, arilo opcionalmente sustituido con uno o más R^{35}, y heteroarilo opcionalmente sustituido con uno o más R^{36};

cada R^{16}, cuando se presenta, es independientemente flúor, -OH, alcoxi inferior, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{17}, cuando se presenta, es independientemente flúor, -OH, alcoxi inferior, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{18} y R^{20}, cuando se presentan, son independientemente hidrógeno, alquilo inferior, o alquilo inferior sustituido con flúor;

cada R^{19}, R^{22}, R^{23}, R^{26}, R^{27}, R^{31} y R^{32}, cuando se presentan, son independientemente alquilo inferior o alquilo inferior sustituido con flúor;

cada R^{21}, cuando se presenta, es flúor, -OH, alcoxi inferior, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{24}, R^{25}, R^{28}, R^{29}, R^{33}, y R^{34}, cuando se presentan, son independientemente alquilo inferior, alquilo inferior sustituido con flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{30}, cuando se presenta, es independientemente flúor, arilo opcionalmente sustituido con uno o más R^{35} o heteroarilo opcionalmente sustituido con uno o más R^{36}; y

cada R^{35} y R^{36}, cuando se presentan, se seleccionan independientemente del grupo que consiste en flúor, cloro, -OH, -NH_2, -CN, -NO_2, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino.

[0005] En algunas modalidades de los compuestos de la Fórmula I:

X es -N= o –C(R^5)=; en donde R^5 se selecciona del grupo que consiste en hidrógeno, flúor, cloro, -CN, alquilo inferior y alcoxi inferior, en donde el alquilo inferior o alcoxi inferior se sustituye opcionalmente con de uno a tres grupos seleccionados de flúor, -OH, alcoxi inferior, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino.

Y se selecciona del grupo que consiste en flúor, cloro, bromo, yodo, alquilo inferior, alcoxi inferior, haloalquilo (por ejemplo, alquilo sustituido con flúor), CN, -OH, cicloalquilo, -OR^8, y –N(R^3)-R^4;

R^1 se selecciona del grupo que consiste en alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilo, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, fenilo opcionalmente sustituido con de uno a tres R^6 (por ejemplo, R^1 es fenilo 2-fluoro-sustituido, fenilo 3-fluoro-sustituido, fenilo 2,5-difluoro-sustituido o fenilo 4-alquilo inferior-sustituido, en donde el alquilo inferior se sustituye opcionalmente con de uno a tres átomos de flúor), y heteroarilo opcionalmente sustituido con uno a tres R^7;

R^2 es hidrógeno, flúor, cloro o alquilo inferior opcionalmente sustituido con uno o más flúor;

R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en (i) hidrógeno, -OR^8 y alquilo inferior opcionalmente sustituido con de uno a tres R^{11}; (ii) cicloalquilo o cicloalquilalquilo, cada uno de los cuales se sustituye opcionalmente con de uno a tres R^{12}; (iii) heterocicloalquilo o heterocicloalquilalquilo, cada uno de los cuales se sustituye opcionalmente con de uno a tres R^{13}; (iv) arilo o arilalquilo, cada uno de los cuales se sustituye opcionalmente con de uno a tres R^{14} opcionalmente, en donde los dos grupos R^{14} adyacentes en el anillo arilo se toman en conjunto para formar un anillo hetero aromático de 5 o 6 miembros que tiene de 1-4 heteroátomos seleccionados de O o N; y (v) heteroarilo o heteroarilalquilo, cada uno de los cuales se sustituye opcionalmente con de uno a tres R^{15};

o R^3 y R^4 son alquilo inferior;

o R^3 y R^4 se combinan con el átomo de nitrógeno al cual se unen para formar un anillo de tres a siete miembros que tiene 0-1 heteroátomo adicional seleccionado de O, N o S, en donde los átomos de nitrógeno y azufre se oxidan opcionalmente;

cada R^6, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, cloro, -CN, -NO_2, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, -C(O)-O-R^{18}, -N(H)-C(O)-R^{19}, y heteroarilo opcionalmente sustituido con

uno o más alquilo inferior; o dos R^6 en carbonos adyacentes se combinan para formar un heterocicloalquilo fusionado opcionalmente sustituido con uno o más alquilo inferior;

cada R^7, cuando se presenta, se selecciona independientemente del grupo que consiste en alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, -C(O)-O-R^{20}, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior;

R^{11}, cuando se presenta, se selecciona del grupo que consiste en cicloalquilo, -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino;

cada R^{14} y R^{15}, cuando se presentan, se seleccionan independientemente del grupo que consiste en flúor, cloro, -CN, -NO_2, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor;

cada R^{18}, cuando se presenta, es independientemente hidrógeno o alquilo inferior;

cada R^{19}, cuando se presenta, es independientemente alquilo inferior; y

cada R^{20}, cuando se presenta, es independientemente hidrógeno o alquilo inferior.

[0006] En algunas modalidades de los compuestos de la Fórmula I, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares. En algunas modalidades, R^1 es alquilo inferior o cicloalquilo (por ejemplo, ciclopropilo), preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares. En algunas modalidades de los compuestos de la Fórmula I, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula I, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares; y R^2 es flúor. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

[0007] En algunas modalidades, X se selecciona del grupo que consiste en –N=, –CH=, -C(CH_3)=, -C(OCH_3)=, -C(F)=, -C(CN)=, -C(CH_2OH)= y –C(Cl)=. En ciertos casos, X es –N=, –CH=, -C(CH_3)=, -C(F)= o -C(CN)=. En una modalidad preferida, X es –N=. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

[0008] En algunas modalidades de los compuestos de la Fórmula I, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares. En algunas modalidades, R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares; R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula I, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares; y R^2 es flúor. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

[0009] En algunas modalidades de los compuestos de la Fórmula I, Y es -OR^8; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares. En algunas modalidades, R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares, y R^8 es hidrógeno, alquilo inferior opcionalmente sustituido con uno o más flúor, o cicloalquilo opcionalmente sustituido con uno o más flúor. En algunas modalidades, R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares, y R^8 es hidrógeno, alquilo inferior opcionalmente sustituido con uno o más flúor, o cicloalquilo opcionalmente sustituido con uno o más flúor; y R^2 es hidrógeno. En algunas modalidades, R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares, y R^8 es hidrógeno o alquilo inferior; y R^2 es flúor. Todas las otras variables son como se define en cualquiera de las modalidades anteriores, o como se describe a continuación.

[0010] En algunas modalidades de los compuestos de la Fórmula I, Y es –$N(R^3)$-R^4; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares. En algunas modalidades de los compuestos de la Fórmula I, Y es –$N(R^3)$-R^4; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula I, Y es –$N(R^3)$-R^4; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares; y R^2 es flúor. En algunas modalidades, R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares, R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en hidrógeno, -OH, alquilo inferior opcionalmente sustituido con R^{11}, cicloalquilo, heterocicloalquilo opcionalmente sustituido con alquilo inferior, fenilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo de 5-6 miembros opcionalmente sustituido con uno o más alquilo inferior, o R^3 y R^4 son alquilo inferior, o R^3 y R^4 se combinan con el nitrógeno al cual se unen para formar un anillo de tres a siete miembros que tiene 0-1 heteroátomo adicional seleccionado de O, N o S, en donde los átomos de nitrógeno y azufre se oxidan opcionalmente, en donde R^{11} y R^{14} son como se define para la Fórmula I, preferiblemente en donde R^{11} se selecciona del grupo que consiste en cicloalquilo, -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino y R^{14} se selecciona del grupo que consiste en flúor, cloro, -CN, -NO_2, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

[0011] En algunas modalidades de los compuestos de la Fórmula I, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino. En algunas modalidades de los compuestos de la Fórmula I, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula I, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es

flúor. En algunas modalidades, R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

[0012] En algunas modalidades de los compuestos de la Fórmula I, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino. En algunas modalidades de los compuestos de la Fórmula I, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es hidrógeno. En algunas modalidades, R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es flúor. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

[0013] En algunas modalidades de los compuestos de la Fórmula I, Y es $-OR^8$; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino. En algunas modalidades de los compuestos de la Fórmula I, Y es $-OR^8$; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula I, Y es $-OR^8$; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es flúor. En algunas modalidades, R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^8 es hidrógeno o alquilo inferior. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

[0014] En algunas modalidades de los compuestos de la Fórmula I, Y es $-N(R^3)-R^4$; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino. En algunas modalidades de los compuestos de la Fórmula I, Y es $-N(R^3)-R^4$; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula I, Y es $-N(R^3)-R^4$; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es flúor. En algunas modalidades, R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino, R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en hidrógeno, -OH, alquilo inferior opcionalmente sustituido con R^{11}, cicloalquilo, heterocicloalquilo opcionalmente sustituido con alquilo inferior, fenilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo de 5-6 miembros opcionalmente sustituido con uno o más alquilo inferior, o R^3 y R^4 son alquilo inferior, o R^3 y R^4 se combinan con el nitrógeno al cual se unen para formar cicloalquilamino, en donde R^{11} y R^{14} son como se define para la Fórmula I, preferiblemente en donde R^{11} se selecciona del grupo que consiste en cicloalquilo, -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino, y R^{14} se selecciona del grupo que consiste en flúor, cloro, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi

inferior sustituido con flúor. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

[0015] En algunas modalidades de los compuestos de la Fórmula I, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. En algunas modalidades de los compuestos de la Fórmula I, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula I, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; y R^2 es flúor. En algunas modalidades, R^1 es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior. En algunas modalidades, R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

[0016] En algunas modalidades de los compuestos de la Fórmula I, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionado del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. En algunas modalidades de los compuestos de la Fórmula I, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionado del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula I, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionado del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; y R^2 es flúor. En algunas modalidades, R^1 es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior. En algunas modalidades, R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

[0017] En algunas modalidades de los compuestos de la Fórmula I, Y is $-OR^8$, R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. En algunas modalidades de los compuestos de la Fórmula I, Y is $-OR^8$, R^1 es fenilo opcionalmente

sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula I, Y is $-OR^8$, R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; y R^2 es flúor. En algunas modalidades, R^1 es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior. En algunas modalidades, R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor, y R^8 es hidrógeno o alquilo inferior. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

[0018] En algunas modalidades de los compuestos de la Fórmula I, Y es $-N(R^3)-R^4$; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. En algunas modalidades, R^1 es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior. En algunas modalidades de los compuestos de la Fórmula I, Y es $-N(R^3)-R^4$; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; y R^2 es hidrógeno. En algunas modalidades, R^1 es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior; y R^2 es flúor. En algunas modalidades, R^1 es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior. En algunas modalidades, R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor, R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en hidrógeno, -OH, alquilo inferior opcionalmente sustituido con R^{11}, cicloalquilo, heterocicloalquilo opcionalmente sustituido con alquilo inferior, fenilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo de 5-6 miembros opcionalmente sustituido con uno o más alquilo inferior, o R^3 y R^4 son alquilo inferior, o R^3 y R^4 se combinan con el nitrógeno al cual se unen para formar cicloalquilamino en donde R^{11} y R^{14} son como se define para la Fórmula I, preferiblemente en donde R^{11} se selecciona del grupo que consiste en cicloalquilo, -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino, y R^{13} se selecciona del grupo que consiste en flúor, cloro, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. En algunas modalidades, R^1 es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior, R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en hidrógeno, -OH, alquilo inferior opcionalmente sustituido con R^{11}, cicloalquilo, heterocicloalquilo opcionalmente sustituido con alquilo inferior, fenilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo de 5-6 miembros opcionalmente sustituido con uno o más alquilo inferior, o R^3 y R^4 son alquilo inferior, o R^3 y

R^4 se combinan con el nitrógeno al cual se unen para formar cicloalquilamino, en donde R^{11} y R^{14} son como se define para la Fórmula I, preferiblemente en donde R^{11} se selecciona del grupo que consiste en cicloalquilo, -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino, y R^{14} se selecciona del grupo que consiste en flúor, cloro, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

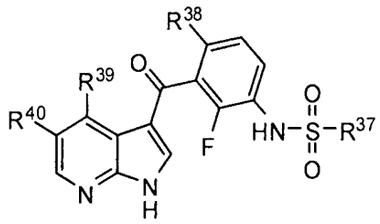
[0019] En algunas modalidades de los compuestos de la Fórmula I, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi. En algunas modalidades de los compuestos de la Fórmula I, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula I, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es flúor. En algunas modalidades, R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

[0020] En algunas modalidades de los compuestos de la Fórmula I, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi. En algunas modalidades de los compuestos de la Fórmula I, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula I, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es flúor. En algunas modalidades, R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

[0021] En algunas modalidades de los compuestos de la Fórmula I, Y es $-OR^8$; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi. En algunas modalidades de los compuestos de la Fórmula I, Y es $-OR^8$; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula I, Y es $-OR^8$; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es flúor. En algunas modalidades, R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi, y R^8 es hidrógeno o alquilo inferior. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

[0022] En algunas modalidades de los compuestos de la Fórmula I, Y es $-N(R^3)-R^4$; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi. En algunas modalidades de los compuestos de la Fórmula I, Y es $-N(R^3)-R^4$; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula I, Y es $-N(R^3)-R^4$; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es flúor. En algunas modalidades, R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi, R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en hidrógeno, -OH, alquilo inferior opcionalmente sustituido con R^{11}, cicloalquilo, heterocicloalquilo opcionalmente sustituido con alquilo inferior, fenilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo de 5-6 miembros opcionalmente sustituido con uno o más alquilo inferior, o R^3 y R^4 son alquilo inferior, o R^3 y R^4 se combinan con el nitrógeno al cual se unen para formar cicloalquilamino, en donde R^{11} y R^{14} son como se define para la Fórmula I, preferiblemente en donde R^{11} se selecciona del grupo que consiste en cicloalquilo, -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino, y R^{14} se selecciona del grupo que consiste en flúor, cloro, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. Todas las otras variables son como se define en cualquiera de las modalidades anteriores o como se describe a continuación.

[0023] En un segundo aspecto, se proporcionan compuestos que tienen la estructura de acuerdo con la siguiente Fórmula II:



Fórmula II

o una sal farmacéuticamente aceptable de los mismos,

en donde:

R^{37} se selecciona del grupo que consiste en alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilo, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, fenilo opcionalmente sustituido con uno o más R^{41} (por ejemplo, R^{37} es fenilo 2-fluoro-sustituido, fenilo 3-fluoro-sustituido, fenilo 2,5-difluoro-sustituido o fenilo 4-alquilo inferior-sustituido, en donde el alquilo inferior se sustituye opcionalmente con uno o más flúor), y heteroarilo opcionalmente sustituido con uno o más R^{42};

R^{38} es hidrógeno, flúor, cloro o alquilo inferior opcionalmente sustituido con uno o más flúor;

R^{39} y R^{40} se seleccionan independientemente del grupo que consiste en flúor, cloro, -CN, -OH, $-NH_2$, alquilo inferior opcionalmente sustituido con uno o más R^{43}, alquenilo inferior opcionalmente sustituido con C(O)-O-R^{44}, alquinilo inferior opcionalmente sustituido con alquilo inferior opcionalmente sustituido con uno o más flúor, o, en un carbono no de alquinilo del mismo, R^{45}, alcoxi inferior opcionalmente sustituido con R^{46}, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino;

cada R^{41}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, cloro, -CN, $-NO^2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, -C(O)-O-R^{47}, -N(H)-C(O)-R^{48}, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior; o dos R^{41} en carbonos adyacentes se combinan para formar un heterocicloalquilo fusionado opcionalmente sustituido con uno o más alquilo inferior;

cada R^{42}, cuando se presenta, se selecciona independientemente del grupo que consiste en alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, -C(O)-O-R^{49}, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior;

cada R^{43}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino;

cada R^{44}, cuando se presenta, es independientemente hidrógeno o alquilo inferior opcionalmente sustituido con uno o más flúor;

cada R^{45}, cuando se presenta, se selecciona independientemente del grupo que consiste en -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino;

cada R^{46}, cuando se presenta, se selecciona independientemente del grupo que consiste en -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino;

cada R^{47}, cuando se presenta, es independientemente hidrógeno o alquilo inferior opcionalmente sustituido con uno o más flúor;

cada R^{48}, cuando se presenta, es independientemente alquilo inferior opcionalmente sustituido con uno o más flúor; y

cada R^{49}, cuando se presenta, es independientemente hidrógeno o alquilo inferior opcionalmente sustituido con uno o más flúor.

[0024] En algunas modalidades de los compuestos de la Fórmula II, R^{37} es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares. En algunas modalidades, R^{37} es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares, R^{39} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior, y R^{40} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior. En algunas modalidades, R^{37} es alquilo inferior, alquilo inferior sustituido con flúor o fenilo, opcionalmente sustituido con de 1-3 grupos R^{41}. En otras modalidades, R^{37} es alquilo inferior, alquilo inferior sustituido con flúor o fenilo sustituido con de 1-3 grupos seleccionados de flúor, cloro, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, $-C(O)-O-R^{47}$ o $-N(H)-C(O)-R^{48}$. Todavía en otras modalidades, R^{37} es alquilo inferior o fenilo sustituido con de 1-2 grupos seleccionados de flúor, cloro, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior o alcoxi inferior sustituido con flúor. En algunas modalidades, R^{37} es alquilo inferior o fenilo opcionalmente sustituido con 1-2 miembros seleccionados de CF_3 o halógeno. En otras modalidades, R^{37} es propilo. Todavía en otras modalidades, R^{37} es 2-trifluorometilfenilo, 3-trifluorometilfenilo, 4-trifluorometilfenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo o fenilo 2,5-difluoro-sustituido. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de la Fórmula II descritos en este documento.

[0025] En algunas modalidades de los compuestos de la Fórmula II, R^{37} es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino. En algunas modalidades, R^{37} es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino, R^{39} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior, y R^{40} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior. En algunas modalidades, R^{37} es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino, R^{39} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior, y R^{40} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior; y R^{38} es hidrógeno. En algunas modalidades, R^{37} es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino, R^{39} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior, y R^{40} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior; y R^{38} es flúor. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de la Fórmula II descritos en este documento.

[0026] En algunas modalidades de los compuestos de la Fórmula II, R^{37} es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. En algunas modalidades, R^{37} es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor, R^{39} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior, y R^{40} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior. En algunas

modalidades, R^{37} es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior. En algunas modalidades, R^{37} es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior, R^{39} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior, y R^{40} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior. En algunas modalidades, R^{37} es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior, R^{39} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior, y R^{40} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior; y R^{38} es hidrógeno. En algunas modalidades, R^{37} es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior, R^{39} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior, y R^{40} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior; y R^{38} es flúor. En algunas modalidades, R^{37} es 4-trifluorometilfenilo, 2-fluorofenilo, 3-fluorofenilo o fenilo 2,5-difluoro-sustituido. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de la Fórmula II descritos en este documento.

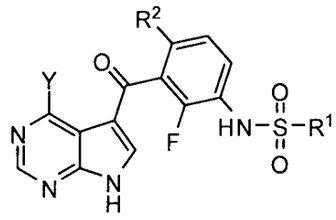
[0027] En algunas modalidades de los compuestos de la Fórmula II, R^{37} es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi. En algunas modalidades, R^{37} es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi, R^{39} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior, y R^{40} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior. En algunas modalidades, R^{37} es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi, R^{39} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior, y R^{40} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior; y R^{38} es hidrógeno. En algunas modalidades, R^{37} es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi, R^{39} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior, y R^{40} es flúor, cloro, -CN, alquilo inferior, o alcoxi inferior; y R^{38} es flúor.

[0028] En algunas modalidades de los compuestos de la Fórmula II, R^{38} es H, -F o alquilo inferior sustituido con flúor. En ciertos casos, R^{38} es H, F o CF_3. En otros casos, R^{38} es F. En otras modalidades, R^{39} es flúor, cloro, -CN, -OH, $-NH_2$, alcoxi inferior, alquilo inferior opcionalmente sustituido con uno o más R^{43}, cicloalquilamino, cicloalquilalquilo-NH-, heterocicloalquilamino y heterocicloalquilálquilo-NH-. En algunas modalidades, R^{39} es flúor, cloro, -CN, -OH, $-NH_2$, alquilo inferior opcionalmente sustituido con flúor, alcoxi inferior, cicloalquilamino, cicloalquilalquilo-NH-, heterocicloalquilamino y heterocicloalquilalquilo-NH-. En modalidades adicionales, R^{39} es flúor, cloro, -CN, -OH, $-NH_2$, CH_3, CH_3O-, CF_3, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclopropilmetilo, ciclobutilmetilo, ciclopentilmetilo, ciclohexilmetilo, ciclopropilamino, ciclobutilamino, ciclopentilamino, ciclohexilamino, ciclopropilmetilamino, ciclobutilmetilamino, ciclopentilmetilamino, ciclohexilmetilamino, 2-tetrahidrofuranilamino, 3-tetrahidrofuranilamino o 4-tetrahidropiranilamino. Todas las otras variables son

como se define en cualquiera de las modalidades de los compuestos de la Fórmula II descritos en este documento.

[0029] En algunas modalidades de los compuestos de la Fórmula II, R^{40} es H, alquilo inferior opcionalmente sustituido con uno o más R^{43}, halógeno, alcoxi inferior o –CN. En algunas modalidades, R^{43} es flúor, -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, ciclopropilamino, ciclobutilamino, ciclopentilamino, ciclohexilamino, cicloheptilamino, 2-tetrahidrofuranilamino, 3-tetrahidrofuranilamino, 2-tetrahidropiranilamino, 3-tetrahidropiranilamino o 4-tetrahidropiranilamino. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de la Fórmula II descritos en este documento.

[0030] En un tercer aspecto, se proporcionan compuestos que tienen la estructura de acuerdo con la siguiente Fórmula III:



Fórmula III

o una sal farmacéuticamente aceptable de los mismos,

en donde Y, R^1 y R^2 en la Fórmula III son como se define en cualquiera de las modalidades de los compuestos de la Fórmula II descritos en este documento. En algunas modalidades:

Y se selecciona del grupo que consiste en flúor, cloro, bromo, yodo, alquilo inferior, alcoxi inferior, haloalquilo, CN, -OH, alquilo sustituido con flúor, cicloalquilo, $-OR^8$, y $-N(R^3)-R^4$;

R^1 se selecciona del grupo que consiste en alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilo, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, fenilo opcionalmente sustituido con uno o más R^6 (por ejemplo, R^1 es fenilo 2-fluoro-sustituido, fenilo 3-fluoro-sustituido, fenilo 2,5-difluoro-sustituido o fenilo 4-alquilo inferior-sustituido, en donde el alquilo inferior se sustituye opcionalmente con uno o más flúor), y heteroarilo opcionalmente sustituido con uno o más R^7;

R^2 es hidrógeno, flúor, cloro o alquilo inferior opcionalmente sustituido con uno o más flúor;

R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en hidrógeno, $-OR^8$, alquilo inferior opcionalmente sustituido con uno o más R^{11}, cicloalquilo opcionalmente sustituido con uno o más R^{12}, heterocicloalquilo opcionalmente sustituido con uno o más R^{13}, arilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo opcionalmente sustituido con uno o más R^{15};

o R^3 y R^4 son alquilo inferior;

o R^3 y R^4 se combinan con el nitrógeno al cual se unen para formar cicloalquilamino;

cada R^6, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, cloro, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, $-C(O)-O-R^{18}$, $-N(H)-C(O)-R^{19}$, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior; o dos R^6 en carbonos adyacentes se combinan para formar un heterocicloalquilo fusionado opcionalmente sustituido con uno o más alquilo inferior;

cada R^7, cuando se presenta, se selecciona independientemente del grupo que consiste en alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, -C(O)-O-R^{20}, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior;

R^8 es hidrógeno, alquilo inferior opcionalmente sustituido con uno o más flúor, o, cuando R^8 es un alquilo C_{2-6}, el alquilo opcionalmente puede sustituirse con uno o más R^{21}; cicloalquilo opcionalmente sustituido con uno o más R^{21}, o heterocicloalquilo opcionalmente sustituido con uno o más R^{21};

cada R^{11}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, cicloalquilo opcionalmente sustituido con uno o más R^{12}, heterocicloalquilo opcionalmente sustituido con uno o más R^{13}, arilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo opcionalmente sustituido con uno o más R^{15};

cada R^{12}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, -N(H)-C(O)-R^{22}, -N(H)-S(O)$_2$-R^{23}, C(O)-R^{24}, y S(O)$_2$-R^{25};

cada R^{13}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, -N(H)-C(O)-R^{26}, -N(H)-S(O)$_2$-R^{27}, C(O)-R^{28}, S(O)$_2$-R^{29}, y alquilo inferior opcionalmente sustituido con uno o más R^{30};

cada R^{14} y R^{15}, cuando se presenta, se seleccionan independientemente del grupo que consiste en flúor, cloro, -OH, -NH_2, -CN, -NO_2, -N(H)-C(O)-R^{31}, -N(H)-S(O)$_2$-R^{32}, C(O)-R^{33}, S(O)$_2$-R^{34}, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, arilo opcionalmente sustituido con uno o más R^{35}, y heteroarilo opcionalmente sustituido con uno o más R^{36};

cada R^{17}, cuando se presenta, es independientemente flúor, -OH, alcoxi inferior, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{18} y R^{20}, cuando se presentan, son independientemente hidrógeno, alquilo inferior, o alquilo inferior sustituido con flúor;

cada R^{19}, R^{22}, R^{23}, R^{26}, R^{27}, R^{31} y R^{32}, cuando se presentan, son independientemente alquilo inferior, alquilo inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{21}, cuando se presenta, es flúor, -OH, alcoxi inferior, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{24}, R^{25}, R^{28}, R^{29}, R^{33}, y R^{34}, cuando se presentan, son independientemente alquilo inferior, alquilo inferior sustituido con flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{30}, cuando se presenta, es independientemente flúor, arilo opcionalmente sustituido con uno o más R^{35} o heteroarilo opcionalmente sustituido con uno o más R^{36}; y

cada R^{35} y R^{36}, cuando se presentan, se seleccionan independientemente del grupo que consiste en flúor, cloro, -OH, $-NH_2$, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino.

[0031] En algunas modalidades de los compuestos de la Fórmula III, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares. En algunas modalidades de los compuestos de la Fórmula III, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula III, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares; y R^2 es flúor. En algunas modalidades, R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0032] En algunas modalidades de los compuestos de la Fórmula III, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares. En algunas modalidades de los compuestos de la Fórmula III, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula III, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares; y R^2 es flúor. En algunas modalidades, R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0033] En algunas modalidades de los compuestos de la Fórmula III, Y es $-OR^8$; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares. En algunas modalidades de los compuestos de la Fórmula III, Y es $-OR^8$; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula III, Y es $-OR^8$; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares; y R^2 es flúor. En algunas modalidades, R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares; R8 es hidrógeno o alquilo inferior. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0034] En algunas modalidades de los compuestos de la Fórmula III, Y es $-N(R^3)-R^4$; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares. En algunas modalidades de los compuestos de la Fórmula III, Y es $-N(R^3)-R^4$; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula III, Y es $-N(R^3)-R^4$; R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares; y R^2 es flúor. En algunas modalidades, R^1 es alquilo inferior o cicloalquilo, preferiblemente alquilo inferior, preferiblemente n-propilo, i-propilo, sec-butilo, i-butilo, y similares, R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en hidrógeno, -OH, alquilo inferior opcionalmente sustituido con R^{11}, cicloalquilo, heterocicloalquilo opcionalmente sustituido con alquilo inferior, fenilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo de 5-6 miembros opcionalmente sustituido con uno o más alquilo inferior, o R^3 y R^4 son alquilo inferior, o R^3 y R^4 se combinan con el nitrógeno al cual se unen para formar cicloalquilamino, en donde R^{11} y R^{14} son como se define para la Fórmula I, preferiblemente en donde R^{11} se selecciona del grupo que consiste en cicloalquilo, -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino, y R^{14} se selecciona del grupo que consiste en flúor, cloro, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0035] En algunas modalidades de los compuestos de la Fórmula III, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino. En algunas modalidades de los compuestos de la Fórmula III, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula III, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es flúor. En algunas modalidades, R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0036] En algunas modalidades de los compuestos de la Fórmula III, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino. En algunas modalidades de los compuestos de la Fórmula III, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula III, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es flúor. En algunas modalidades, R^1 es mono-alquilamino, di-alquilamino, o

cicloalquilamino, preferiblemente di-alquilamino, cicloalquilamino, o heterocicloalquilamino. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0037] En algunas modalidades de los compuestos de la Fórmula III, Y es $-OR^8$; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino. En algunas modalidades de los compuestos de la Fórmula III, Y es $-OR^8$; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula III, Y es $-OR^8$; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es flúor. En algunas modalidades, R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^8 es hidrógeno o alquilo inferior. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0038] En algunas modalidades de los compuestos de la Fórmula III, Y es $-N(R^3)-R^4$; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino. En algunas modalidades de los compuestos de la Fórmula III, Y es $-N(R^3)-R^4$; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula III, Y es $-N(R^3)-R^4$; R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino; y R^2 es flúor. En algunas modalidades, R^1 es mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino, preferiblemente di-alquilamino o cicloalquilamino, R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en hidrógeno, -OH, alquilo inferior opcionalmente sustituido con R^{11}, cicloalquilo, heterocicloalquilo opcionalmente sustituido con alquilo inferior, fenilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo de 5-6 miembros opcionalmente sustituido con uno o más alquilo inferior, o R^3 y R^4 son alquilo inferior, o R^3 y R^4 se combinan con el nitrógeno al cual se unen para formar cicloalquilamino, en donde R^{11} y R^{14} son como se define para la Fórmula I, preferiblemente en donde R^{11} se selecciona del grupo que consiste en cicloalquilo, -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino, y R^{14} se selecciona del grupo que consiste en flúor, cloro, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0039] En algunas modalidades de los compuestos de la Fórmula III, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. En algunas modalidades de los compuestos de la Fórmula III, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; y R^2 es hidrógeno. En

algunas modalidades de los compuestos de la Fórmula III, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; y R^2 es flúor. En algunas modalidades, R^1 es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior. En algunas modalidades, R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0040] En algunas modalidades de los compuestos de la Fórmula III, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionado del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. En algunas modalidades de los compuestos de la Fórmula III, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionado del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula III, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionado del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; y R^2 es flúor. En algunas modalidades, R^1 es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior. En algunas modalidades, R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0041] En algunas modalidades de los compuestos de la Fórmula III, Y is $-OR^8$, R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. En algunas modalidades, R^1 es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior. En algunas modalidades de los compuestos de la Fórmula III, Y is $-OR^8$, R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. En algunas modalidades, R^1 es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior. En algunas modalidades de los compuestos de la Fórmula III, Y is $-OR^8$, R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; y R^2 es hidrógeno. En algunas modalidades, R^1 es fenilo

mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior; y R^2 es flúor. En algunas modalidades, R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor, y R^8 es hidrógeno o alquilo inferior. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0042] En algunas modalidades de los compuestos de la Fórmula III, Y es $-N(R^3)-R^4$; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. En algunas modalidades de los compuestos de la Fórmula III, Y es $-N(R^3)-R^4$; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula III, Y es $-N(R^3)-R^4$; R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; y R^2 es flúor. En algunas modalidades, R^1 es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior. En algunas modalidades, R^1 es fenilo opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor, R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en hidrógeno, -OH, alquilo inferior opcionalmente sustituido con R^{11}, cicloalquilo, heterocicloalquilo opcionalmente sustituido con alquilo inferior, fenilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo de 5-6 miembros opcionalmente sustituido con uno o más alquilo inferior, o R^3 y R^4 son alquilo inferior, o R^3 y R^4 se combinan con el nitrógeno al cual se unen para formar cicloalquilamino en donde R^{11} y R^{14} son como se define para la Fórmula I, preferiblemente en donde R^{11} se selecciona del grupo que consiste en cicloalquilo, -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino, y R^{13} se selecciona del grupo que consiste en flúor, cloro, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. En algunas modalidades, R^1 es fenilo mono-sustituido con flúor, alquilo inferior, o $-CF_3$, o di-sustituido con dos flúor, dos alquilo inferior, o un flúor y un alcoxi inferior, R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en hidrógeno, -OH, alquilo inferior opcionalmente sustituido con R^{11}, cicloalquilo, heterocicloalquilo opcionalmente sustituido con alquilo inferior, fenilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo de 5-6 miembros opcionalmente sustituido con uno o más alquilo inferior, o R^3 y R^4 son alquilo inferior, o R^3 y R^4 se combinan con el nitrógeno al cual se unen para formar cicloalquilamino, en donde R^{11} y R^{14} son como se define para la Fórmula I, preferiblemente en donde R^{11} se selecciona del grupo que consiste en cicloalquilo, -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino, y R^{14} se selecciona del grupo que consiste en flúor, cloro, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0043] En algunas modalidades de los compuestos de la Fórmula III, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi. En algunas modalidades de los compuestos de la Fórmula III, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula III, Y es flúor, cloro, bromo, o yodo, preferiblemente flúor; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es flúor. En algunas modalidades, R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0044] En algunas modalidades de los compuestos de la Fórmula III, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi. En algunas modalidades de los compuestos de la Fórmula III, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula III, Y es alquilo inferior, alquilo sustituido con flúor, o cicloalquilo; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es flúor. En algunas modalidades, R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

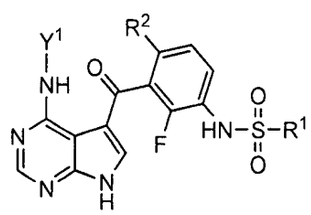
[0045] En algunas modalidades de los compuestos de la Fórmula III, Y es $-OR^8$; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi. En algunas modalidades de los compuestos de la Fórmula III, Y es $-OR^8$; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula III, Y es $-OR^8$; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente

seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es flúor. En algunas modalidades, R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi, y R^8 es hidrógeno o alquilo inferior. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0046] En algunas modalidades de los compuestos de la Fórmula III, Y es $-N(R^3)-R^4$; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi. En algunas modalidades de los compuestos de la Fórmula III, Y es $-N(R^3)-R^4$; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es hidrógeno. En algunas modalidades de los compuestos de la Fórmula III, Y es $-N(R^3)-R^4$; R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi; y R^2 es flúor. En algunas modalidades, R^1 es heteroarilo de 5-6 miembros opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo inferior y alcoxi inferior, preferiblemente piridinilo mono- o di-sustituido con metoxi, R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en hidrógeno, -OH, alquilo inferior opcionalmente sustituido con R^{11}, cicloalquilo, heterocicloalquilo opcionalmente sustituido con alquilo inferior, fenilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo de 5-6 miembros opcionalmente sustituido con uno o más alquilo inferior, o R^3 y R^4 son alquilo inferior, o R^3 y R^4 se combinan con el nitrógeno al cual se unen para formar cicloalquilamino, en donde R^{11} y R^{14} son como se define para la Fórmula I, preferiblemente en donde R^{11} se selecciona del grupo que consiste en cicloalquilo, -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino, y R^{14} se selecciona del grupo que consiste en flúor, cloro, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0047] En algunas modalidades de los compuestos de las Fórmulas I, II y III, Y es flúor, cloro, bromo, yodo, alquilo inferior, alcoxi inferior, haloalquilo, CN, -OH, cicloalquilo, $-OR^8$ o $-NH(R^4)$. En una modalidad preferida, Y es CH_3, etilo, metoxi, etioxi, isobutilo, CN, OH, F, Cl, Br, I, NH_2, butioxi, 2-metilpropoxi, 4-tetrahidropiraniloxi, 2-tetrahirofuraniloxi, 3-tetrahirofuraniloxi, alcoxiamino o HO-NH-.

[0048] En otros aspectos, la invención proporciona un compuesto que tiene la sub-Fórmula IIIa:



IIIa

en donde Y^1 es alquilo inferior opcionalmente sustituido con de uno a tres R^{11}, cicloalquilo, cicloalquilalquilo, arilo, arilalquilo, heterocicloalquilo, heterocicloalquilalquilo, heteroarilo o heteroarilalquilo, en donde:
el cicloalquilo y cicloalquilalquilo se sustituyen cada uno opcionalmente con de uno a tres R^{12};
el heterocicloalquilo y heterocicloalquilalquilo se sustituyen cada uno opcionalmente con de uno a tres R^{13};
el arilo y arilalquilo se sustituyen cada uno opcionalmente con de uno a tres R^{14} opcionalmente, en donde los dos grupos R^{14} adyacentes en el anillo arilo se toman en conjunto para formar un anillo hetero aromático de 5 o 6 miembros que tiene de 1-4 heteroátomos seleccionados de O o N; y el heteroarilo y heteroarilalquilo se sustituyen cada uno opcionalmente con de uno a tres R^{15}. Las otras variables R^1 y R^2 son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II y III descritos en este documento.

[0049] En algunas modalidades de los compuestos de la Fórmula IIIa, Y^1 se selecciona de alquilo inferior, alquilo inferior sustituido con halógeno, 2-hidroxietilo, ciclopropilamino, ciclobutilo, ciclopropilmetilo, ciclobutilmetilo, ciclopentilo, ciclopentilmetilo, ciclohexilmetilo, ciclohexilo, 2-oxetanilo, 2-oxetanilmetilo, 3-oxetanilo, 3-oxetanilmetilo, 2-tetrahidrofuranilo, 3-tetrahidrofuranilo, 2-tetrahidropiranilo, 3-tetrahidropiranilo, 4-tetrahidropiranilo, 2-tetrahidrofuranilmetilo, 3-tetrahidrofuranilmetilo, 2-tetrahidropiranilmetilo, 3-tetrahidropiranilmetilo, 4-tetrahidropiranilmetilo, 1-metil-2-aziridinilo, 1-metil-2-aziridinilmetilo, 1-metil-2-azetidinilo, 1-metil-2-azetidinilmetilo, 1-metil-3-azetidinilo, 1-metil-3-azetidinilmetilo, 1-metil-2-pirrolidinilo, 1-metil-2-pirrolidinilmetilo, 1-metil-3-pirrolidinilo, 1-metil-3-pirrolidinilmetilo, 1-metil-2-piperidinilo, 1-metil-2-piperidinilmetilo, 1-metil-3-piperidinilo, 1-metil-3-piperidinilmetilo, 1-metil-4-piperidinilo, 1-metil-4-piperidinilmetilo, 1-metilsulfonil-2-piperidinilo, 1-metilsulfonil-2-piperidinilmetilo, 1-metilsulfonil-3-piperidinilo, 1-metilsulfonil-3-piperidinilmetilo, 1-metilsulfonil-4-piperidinilo, 1-metilsulfonil-4-piperidinilmetilo, 1,1-dioxo-4-tianilo, 1,1-dioxo-4-tianilmetilo, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-bencilo, 2-fluorobencilo, 3-fluorobencilo, 4-fluorobencilo, 2-piridilo, 2-piridilmetilo, 3-piridilo, 3-piridilmetilo, 4-piridilo, 4-piridilmetilo, 2-clorofenilo, 3-clorofenilo, 4-clorofenilo, 2-dimetilaminofenilo, 3-dimetilaminofenilo, 4-dimetilaminofenilo, 2-dimetilaminobencilo, 2-dimetilaminobencilo, 3-dimetilaminobencilo, 4-dimetilaminobencilo, 2-hidoxifenilo, 3-hidoxifenilo, 4-hidoxifenilo, 2-hidroxibencilo, 3-hidroxibencilo, 4-hidroxibencilo, 2-carboxifenilo, 3-carboxifenilo, 4-carboxifenilo, 2-carboxibencilo, 3-carboxibencilo, 4-carboxibencilo, 2-metoxicarbonilfenilo, 3-metoxicarbonilfenilo, 4-metoxicarbonilfenilo, 2-metoxicarbonilbencilo, 3-metoxicarbonilbencilo, 4-metoxicarbonilbencilo, 1-alquil-4-pirazolilo, 1-alquil-4-pirazolilmetilo, 3-piridazinilo, piridazinilmetilo, 4-piridazinilo, 4-piridazinilmetilo, triazolilo, triazolimetilo, tetrazolilo, tetrazolimetilo, 2,1,3,-benzoxadiazolilo, 2,1,3-benzoxadiazol-5-ilo, 2,1,3,-benzoxadiazolil-metilo, 2,1,3-benzoxadiazol-5ilmetilo, 2,1,3,-benzotiadiazolilo, 2,1,3-benzotiadiazol-5-ilo, 2,1,3,-benzotiadiazolil-metilo, 2,1,3-benzotiadiazol-5ilmetilo, 1H-1,2,4-triazol-5-ilo, 1H-1,2,4-triazol-5-metilo, 2-oxobencimidazol-4-ilo, 2-oxobencimidazol-4-metilo, 2-oxobencimidazol-5-ilo, 2-oxobencimidazol-5-metilo, 1,1,-dioxo-tiolan-3-ilo, 1,1-dioxotiolan-3-metilo, 3-(2-metil-1,2,3,4-tetrazol-5-il)fenilo, 3-(2-metil-1,2,3,4-tetrazol-5-il)bencilo, 3-(5-metil-1,2,3,4-tetrazol-1-il)fenilo, 3-(1,2,4-triazol-5-il)fenilo, 3-(1,2,,4-triazol-5-il)bencilo, 3-3-metil-4H-1,2,4-

triazol-5-metilo o 2-(3-metil-4H-1,2,4-triazol-5-il)etilo. En ciertos casos, Y^1 es ciclopropilmetilo. Las otras variables R^1 y R^2 son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II, III y IIIa descritos en este documento.

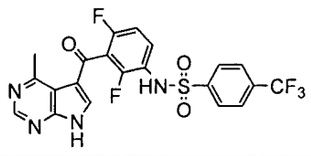
[0050] En algunas modalidades de los compuestos de la Fórmula IIIa, R^2 es H o F. Las otras variables R^1 y Y^1 son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II, III y IIIa descritos en este documento.

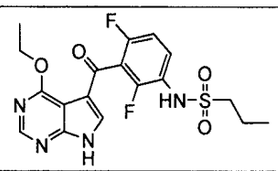
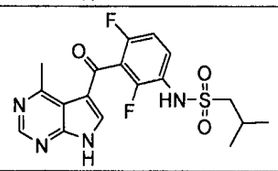
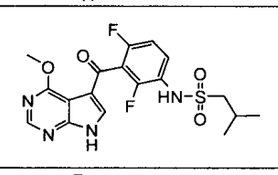
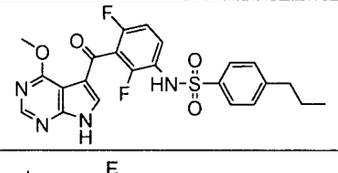
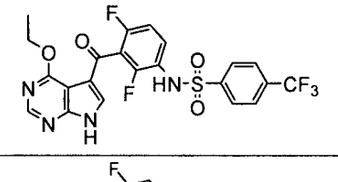
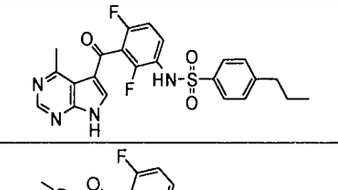
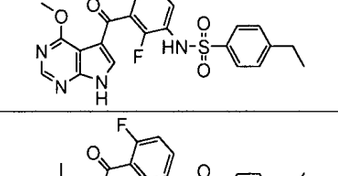
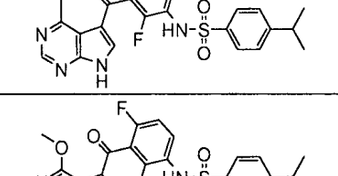
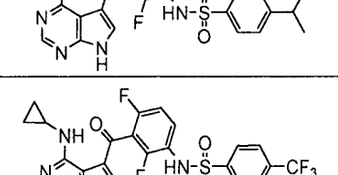
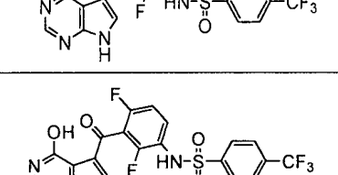
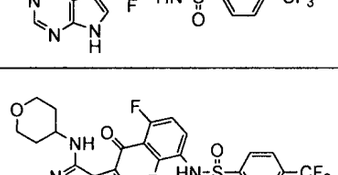
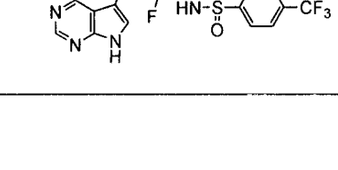
[0051] En algunas modalidades de los compuestos de las Fórmulas I, II, III and IIIa, R^1 es alquilo inferior, cicloalquilo opcionalmente sustituido con 1-2 grupos seleccionados de halógeno o alquilo inferior, heterocicloalquilo, heteroarilo opcionalmente sustituido con alquilo inferior o alcoxi inferior, fenilo opcionalmente sustituido con 1-2 sustituyentes seleccionados de alquilo inferior, halógeno, alcoxi inferior, haloalquilo, haloalcoxi o CN. En algunas modalidades, R^1 es metilo, propilo, isobutilo, 2-metilpropilo, CF_3, CF_3CH_2-, CHF_2CH_2-, 4-trifluorofenilo, 2-trifluorofenilo, 3-trifluorofenilo, 3,5-dimetilfenilo, 4-propilfenilo, 3-fluoro-4-metoxifenilo, 2-cianofenilo, 3-cianofenilo, 4-cianofenilo, 4-fluoro-3-metoxifenilo, 2,5-difluorofenilo, 2,6-difluorofenilo, 2,4-difluorofenilo, 2-piridilo, 3-piridilo, 5-metoxi-2-piridilo, 3-metoxi-2-piridilo, 4-metoxi-2-piridilo, 6-metil-2-piridilo, 5-metil-2-piridilo, 4-metil-2-piridilo, 3-metil-2-piridilo, dialquilamino, 1-pirrolidinilo, 1-piperidinilo, 4-morfolinilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, 4,4-difluorociclohexilo, 1-metil-4-pirazolilo, 1-etil-4-pirazolilo, 1-metil-3-pirazolilo, 1-etil-3-pirazolilo, 6-metil-3-piridilo, 5-metil-3-piridilo, 4-metil-3-piridilo o 2-metil-3-piridilo. En una modalidad adicional, R^1 es 2-fluorofenilo, 3-fluorofenilo, 2,5-difluorofenilo o fenilo 4-alquilo inferior-sustituido, en donde el alquilo inferior se sustituye opcionalmente con uno o más flúor. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II, III y IIIa descritos en este documento.

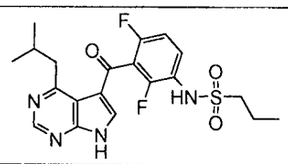
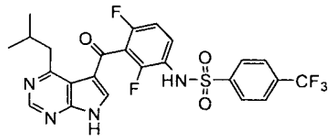
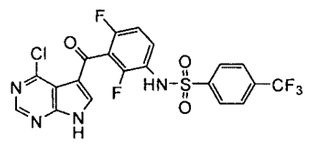
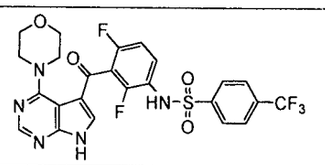
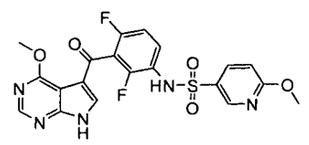
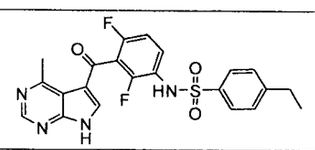
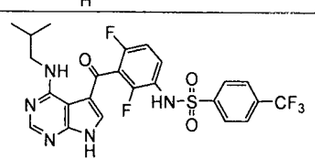
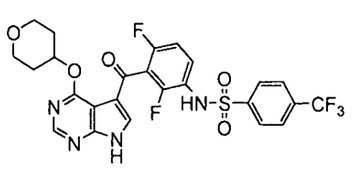
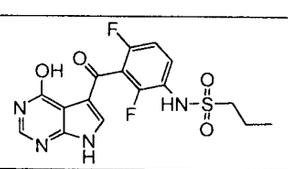
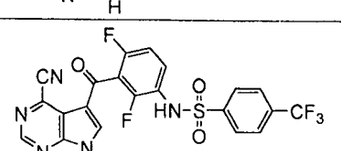
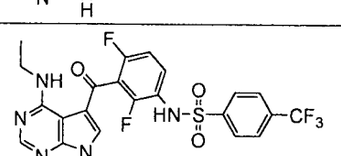
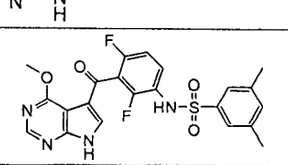
[0052] En un grupo particular de modalidades de los compuestos de las Fórmulas I, II, III y IIIa, Y es $-NR^3R^4$, en donde R^3 y R^4 se combinan con el átomo de nitrógeno al cual se unen para formar un anillo de tres a siete miembros que tiene 0-1 heteroátomo de anillo adicional seleccionado de O, N o S, en donde el átomo de nitrógeno o azufre se oxida opcionalmente. En ciertos casos, Y es 1-aziridinilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidinilo, 1-morfolinilo o 1-azepanilo. Todas las otras variables son como se define en cualquiera de las modalidades de los compuestos de las Fórmulas I, II, III y IIIa descritos en este documento.

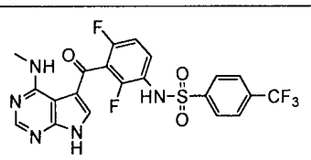
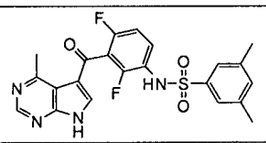
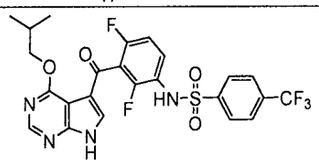
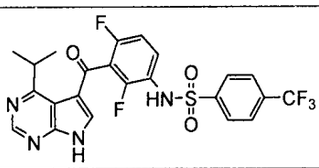
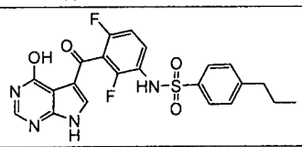
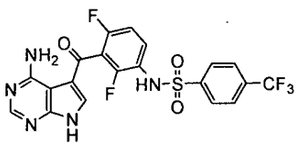
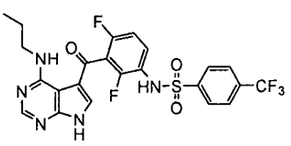
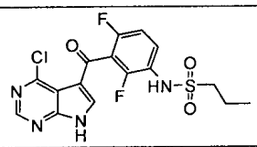
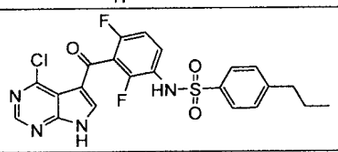
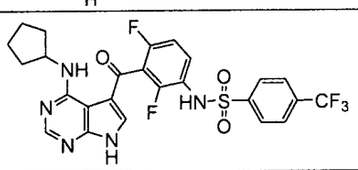
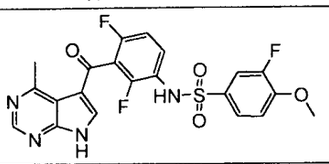
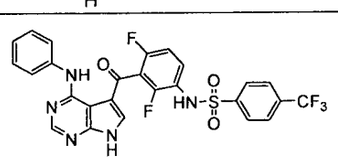
[0053] En diversos aspectos y modalidades, se proporcionan los compuestos mostrados en la Tabla I a continuación, y/o sales farmacéuticamente aceptables de los compuestos mostrados en la Tabla I.

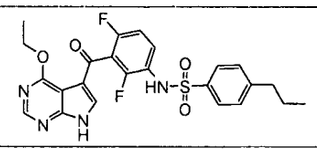
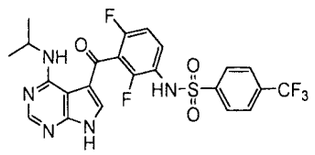
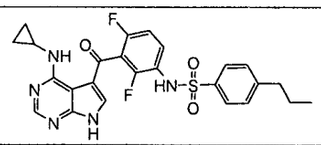
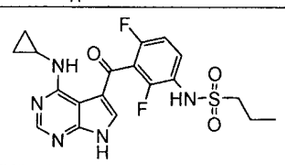
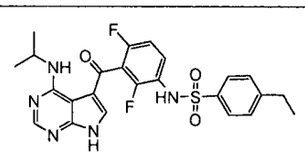
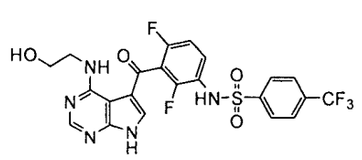
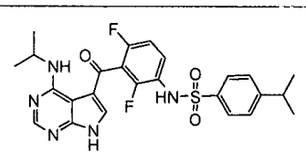
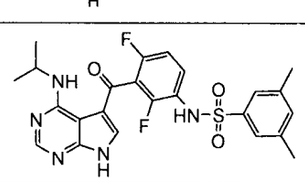
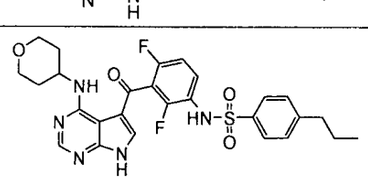
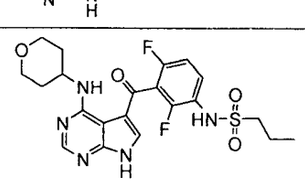
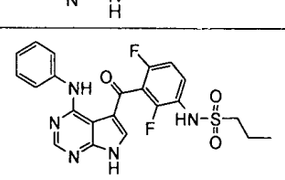
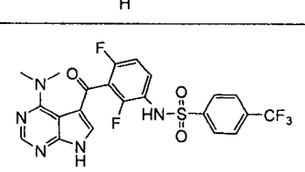
Tabla I

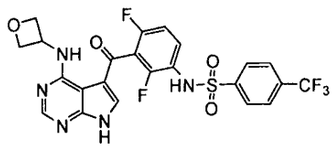
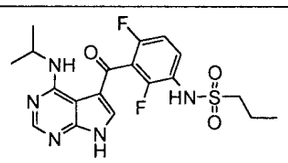
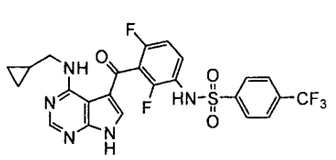
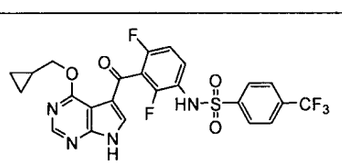
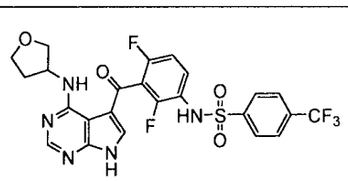
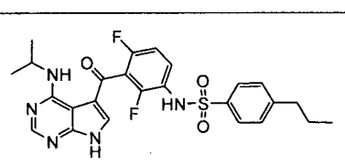
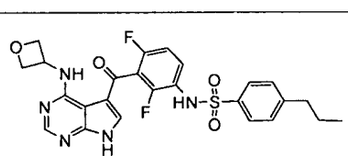
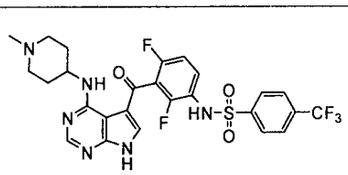
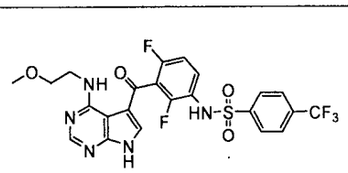
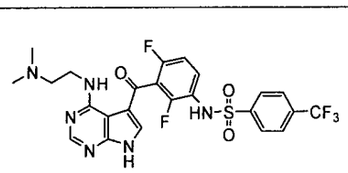
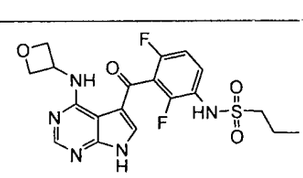
Comp. #	Estructura	Nombre	MS
P-1001		N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida	496.9

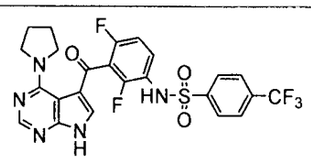
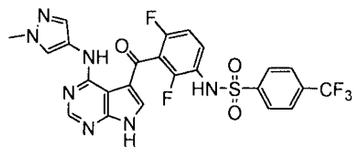
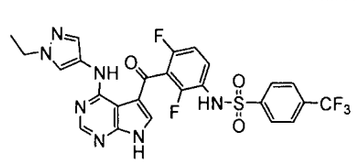
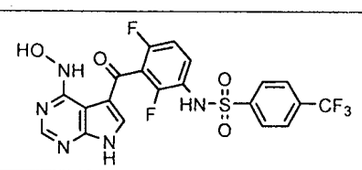
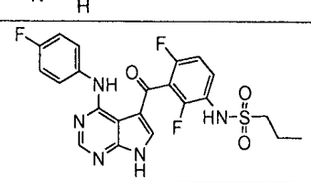
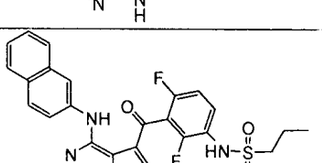
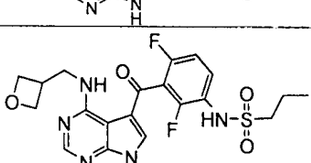
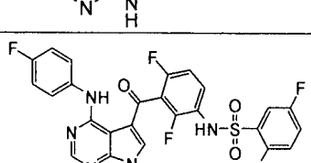
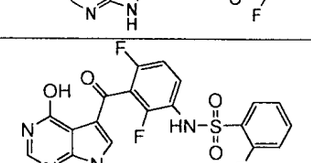
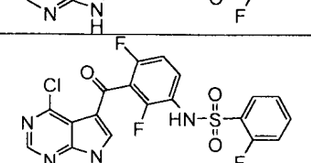
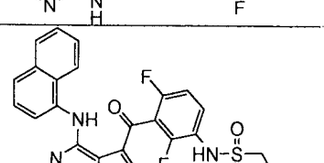
P-1002		[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida del ácido propano-1-sulfónico	424.9
P-1003		[2,4-difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida del ácido 2-metil-propano-1-sulfónico	409.3
P-1004		[2,4-difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida del ácido 2-metil-propano-1-sulfónico	425.1
P-1005		N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida	486.95
P-1006		N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida	526.95
P-1007		N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida	470.95
P-1008		N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida	473.0
P-1009		N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida	471.3
P-1010		N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida	486.8
P-1011		N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida	537.8
P-1012		N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida	499.0
P-1013		N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida	581.8; 582.0

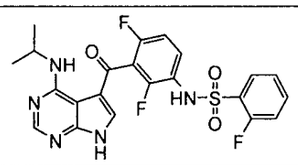
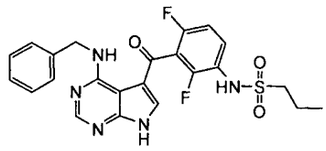
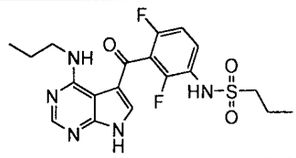
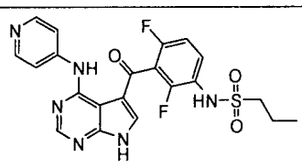
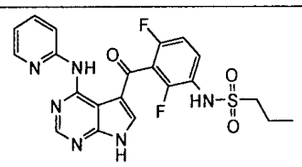
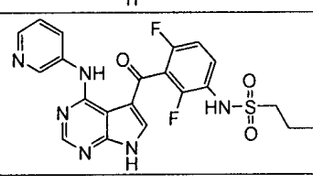
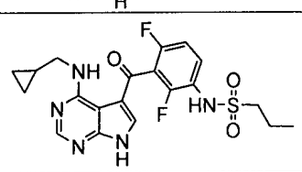
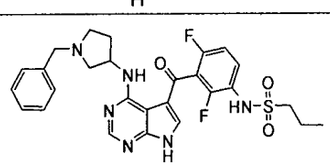
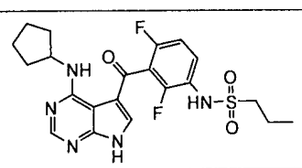
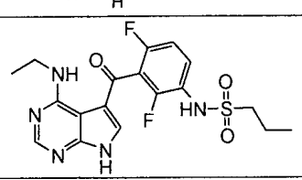
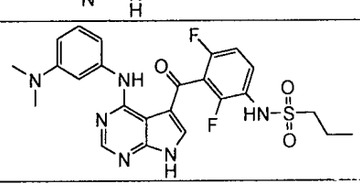
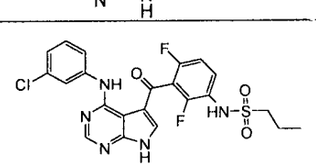
P-1014		[2,4-Difluoro-3-(4-isobutil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida del ácido propano-1-sulfónico	436.7
P-1015		N-[2,4-Difluoro-3-(4-isobutil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida	538.6
P-1016		N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida	516.9
P-1017		N-[2,4-Difluoro-3-(4-morfolin-4-il-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida	567.8
P-1018		[2,4-difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida del ácido 6-metoxi-piridin-3-sulfónico	476.0
P-1019		N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida	457.2
P-1020		N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida	554.4; 554.0
P-1021		N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-iloxi)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida	581.2
P-1022		[2,4-difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida del ácido propano-1-sulfónico	397.0
P-1023		N-[3-(4-Ciano-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida	508.1
P-1024		N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida	525.95
P-1025		N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3,5-isopropil-bencenosulfonamida	473.0

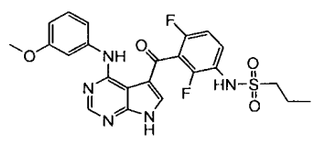
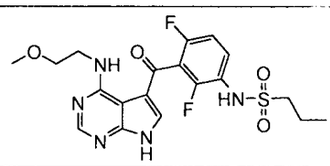
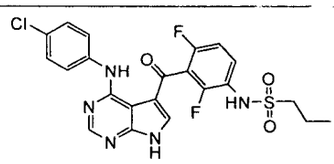
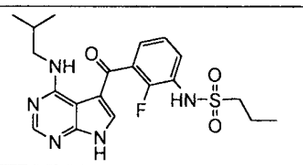
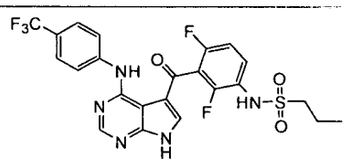
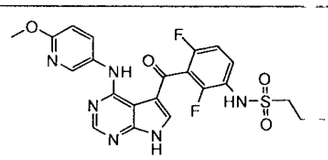
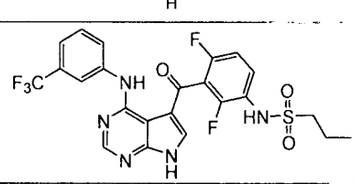
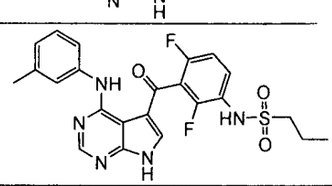
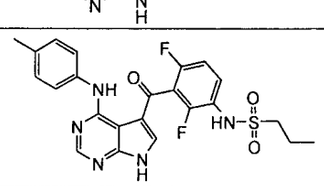
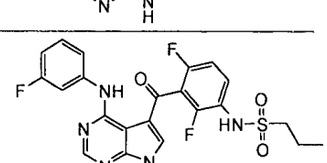
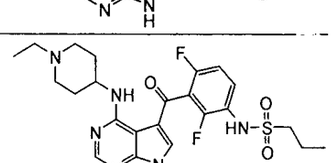
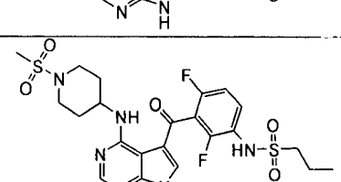
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P-1027		N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3,5-dimetil-bencenosulfonamida	456.95
P-1028		N-[2,4-Difluoro-3-(4-isobutoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida	553.2
P-1029		N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida	525.2
P-1030		N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida	472.9
P-1031		N-[3-(4-Amino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida	497.9
P-1032		N-[2,4-Difluoro-3-(4-propilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida	539.95
P-1033		[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida del ácido propano-1-sulfónico	414.8
P-1034		N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida	490.9
P-1035		N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida	566.3
P-1036		N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-fluoro-4-metoxi-bencenosulfonamida	477.0
P-1037		N-[2,4-Difluoro-3-(4-fenilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida	573.9

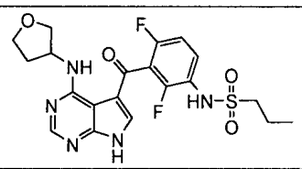
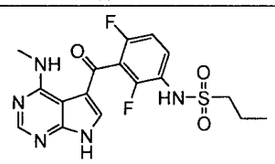
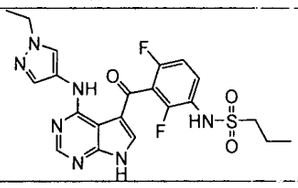
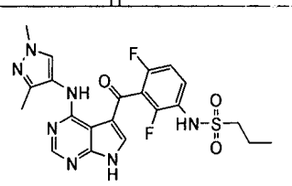
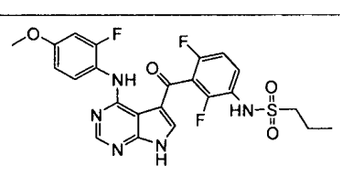
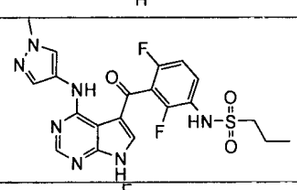
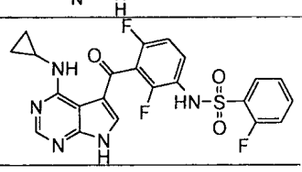
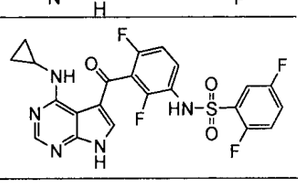
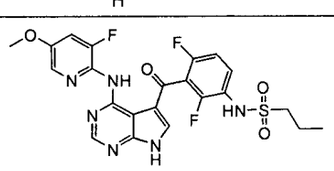
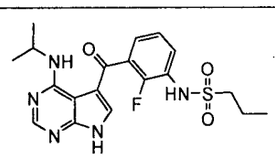
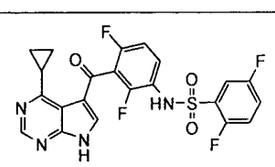
P-1038		N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida	501.0
P-1039		N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida	540.0
P-1040		N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida	512.0
P-1041		[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida del ácido propano-1-sulfónico	435.95
P-1042		N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida	500.27
P-1043		N-{2,4-Difluoro-3-[4-(2-hidroxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida	541.95
P-1044		N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida	514.0
P-1045		N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3,5-dimetil-bencenosulfonamida	500.05
P-1046		N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-propil-bencenosulfonamida	556.0
P-1047		{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida del ácido propano-1-sulfónico	479.95
P-1048		[2,4-difluoro-3-(4-fenilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida del ácido propano-1-sulfónico	473.95
P-1049		N-[3-(4-Dimetilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida	525.95

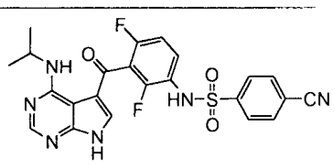
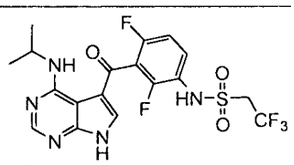
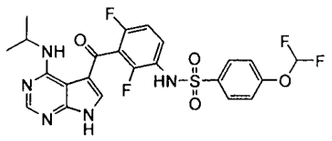
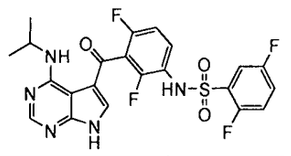
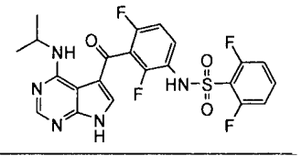
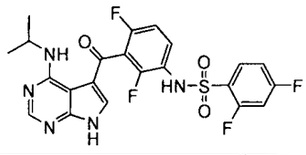
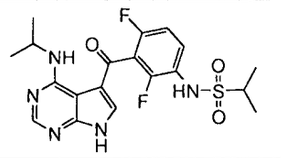
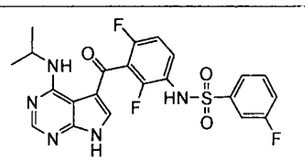
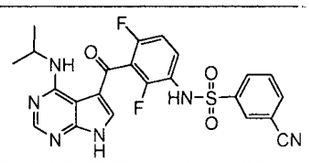
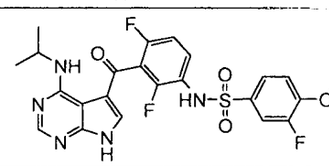
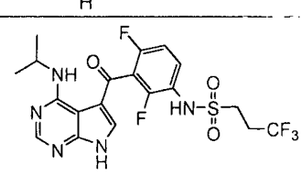
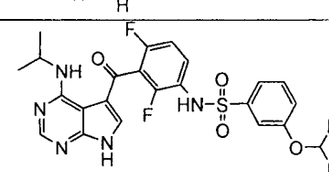
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P-1051		[2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida del ácido propano-1-sulfónico	437.95
P-1052		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida	552.2
P-1053		N-[3-(4-Ciclopropilmetoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida	553.2
P-1054		N-{2,4-Difluoro-3-[4-(tetrahidro-furan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida	568.0
P-1055		N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida	514.0
P-1056		N-{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-propil-bencenosulfonamida	528.0
P-1057		N-{2,4-Difluoro-3-[4-(1-metil-piperidin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida	595.0
P-1058		N-{2,4-Difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida	556.3
P-1059		N-{3-[4-(2-Dimetilamino-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida	569.5
P-1060		{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida del ácido propano-1-sulfónico	451.95

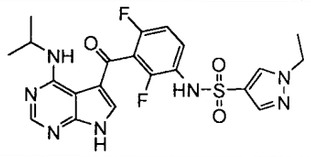
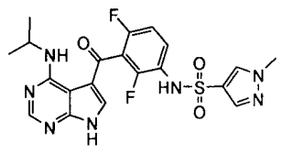
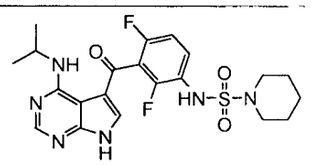
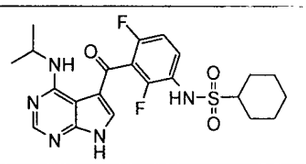
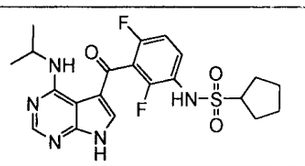
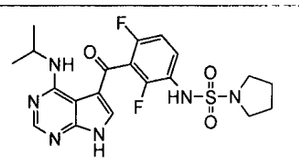
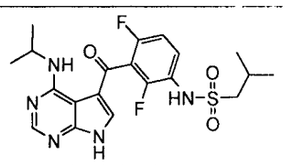
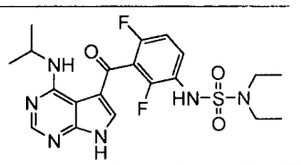
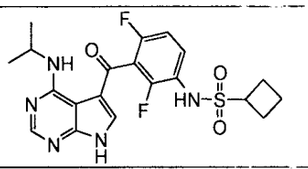
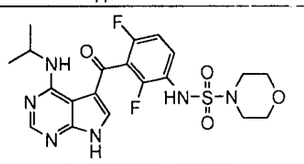
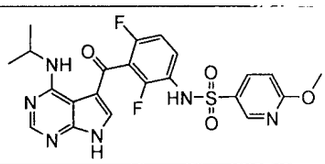
P-1061		N-[2,4-Difluoro-3-(4-pirrolidin-1-il-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida	552.5
P-1062		N-{2,4-Difluoro-3-[4-(1-metil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida	578.1
P-1063		N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida	592.5
P-1064		N-[2,4-Difluoro-3-(4-hidroxiamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida	513.9
P-1065		{2,4-Difluoro-3-[4-(4-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida del ácido propano-1-sulfónico	490.0
P-1067		{2,4-Difluoro-3-[4-(naftalen-2-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida del ácido propano-1-sulfónico	522.25
P-1068		(2,4-difluoro-3-{4-[(oxetan-3-ilmetil)-amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida del ácido propano-1-sulfónico	513.9
P-1069		N-{2,4-Difluoro-3-[4-(4-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida	559.9
P-1070		N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida	448.9
P-1071		N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida	466.9/ 468.9
P-1072		{2,4-Difluoro-3-[4-(naftalen-1-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida del ácido propano-1-sulfónico	522.0

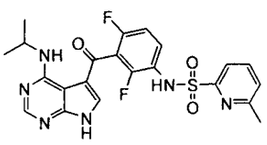
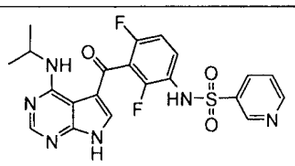
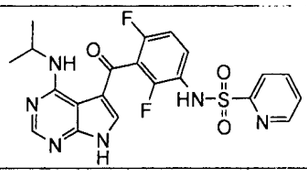
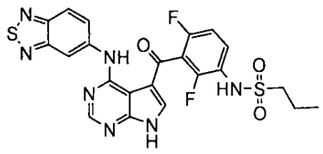
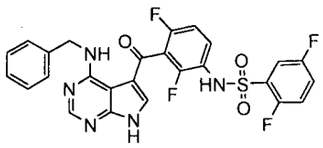
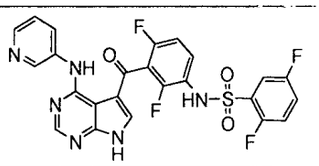
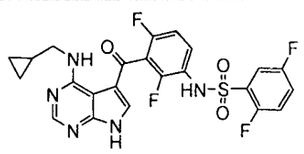
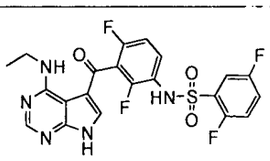
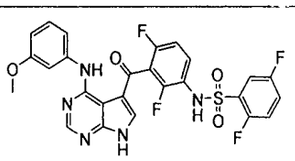
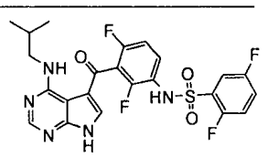
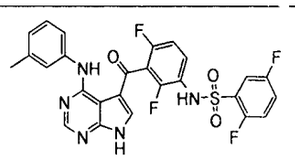
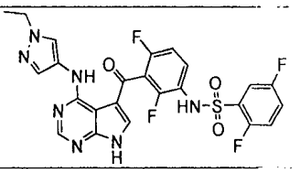
P-1073		N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida	490.0
P-1074		[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida del ácido propano-1-sulfónico	486.5
P-1075		[2,4-Difluoro-3-(4-propilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida del ácido propano-1-sulfónico	438.0
P-1076		{2,4-Difluoro-3-[4-(piridin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida del ácido propano-1-sulfónico	473.0
P-1077		{2,4-Difluoro-3-[4-(piridin-2-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida del ácido propano-1-sulfónico	473.0
P-1078		{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida del ácido propano-1-sulfónico	473.0
P-1079		{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida del ácido propano-1-sulfónico	450.0
P-1080		{3-[4-(1-Bencil-pirrolidin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida del ácido propano-1-sulfónico	555.5
P-1081		[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida del ácido propano-1-sulfónico	464.0
P-1082		[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida del ácido propano-1-sulfónico	424.0
P-1083		{3-[4-(3-Dimetilamino-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida del ácido propano-1-sulfónico	515.5
P-1084		{3-[4-(3-cloro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida del ácido propano-1-sulfónico	506.0

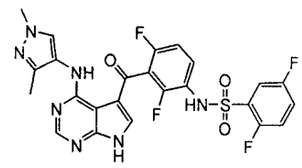
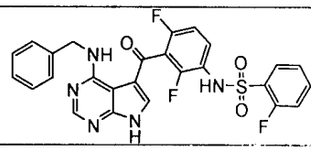
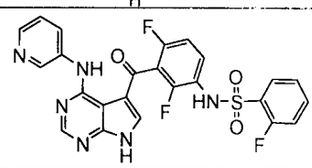
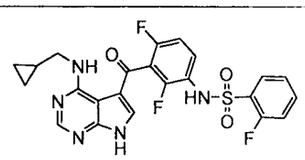
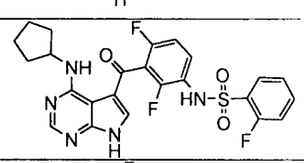
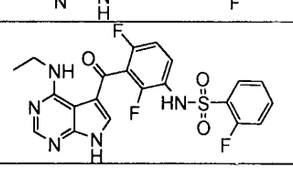
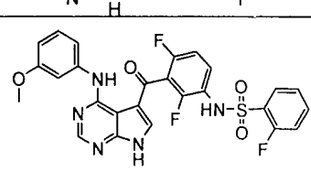
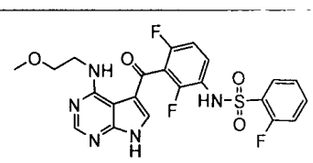
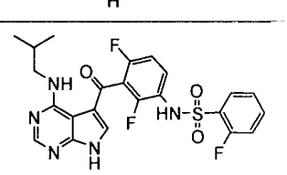
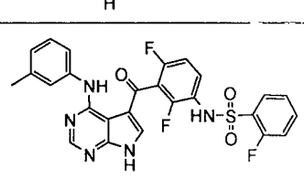
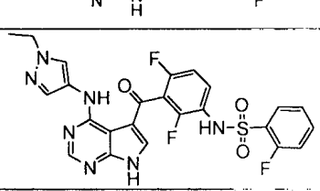
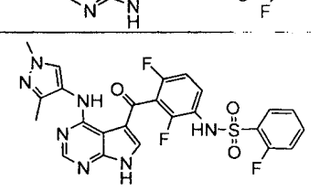
P-1085		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	502.5
P-1086		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	454.0
P-1087		Ácido propano-1-sulfónico {3-[4-(4-cloro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	506.0
P-1088		Ácido propano-1-sulfónico [2,4-difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	452.0
P-1089		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(4-trifluorometil-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	540.5
P-1090		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(6-metoxi-piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	503.0
P-1091		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-trifluorometil-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	540.5
P-1092		Ácido propano-1-sulfónico [2,4-difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	486.5
P-1093		Ácido propano-1-sulfónico [2,4-difluoro-3-(4-p-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	486.5
P-1094		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	490.5
P-1095		Ácido propano-1-sulfónico {3-[4-(1-etil-piperidin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	507.5
P-1096		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1-metanosulfonil-piperidin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-	557.5

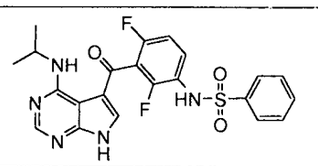
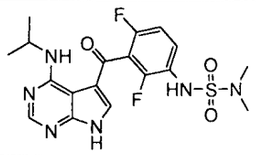
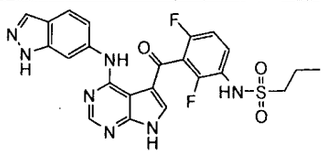
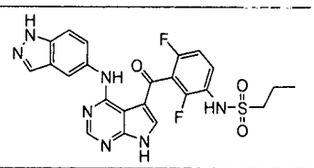
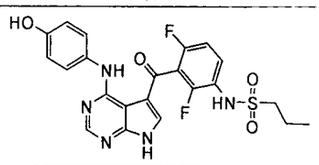
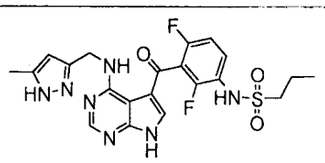
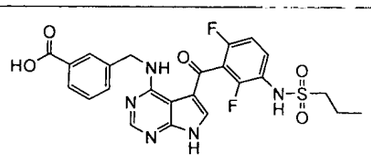
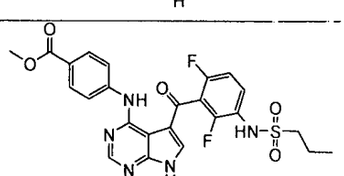
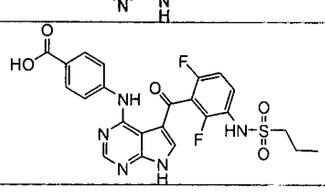
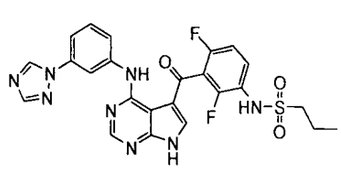
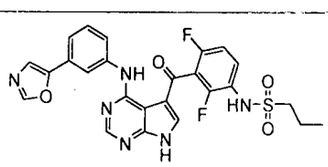
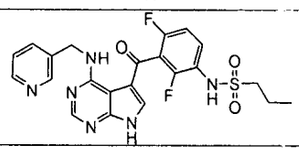
		fenil}-amida	
P-1097		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(tetrahidro-furan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	466.5
P-1098		Ácido propano-1-sulfónico [2,4-difluoro-3-(4-metilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	410.0
P-1099		Ácido propano-1-sulfónico {3-[4-(1-etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	490.5
P-1100		Ácido propano-1-sulfónico {3-[4-(1,3-dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	490.5
P-1101		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(2-fluoro-4-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	520.5
P-1102		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1-metil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	476.0
P-1103		N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida	488.0
P-1104		N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida	506.0
P-1105		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-fluoro-5-metoxi-piridin-2-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	521.0
P-1106		Ácido propano-1-sulfónico [2-fluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	420.0
P-1107		N-[3-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida	491.4

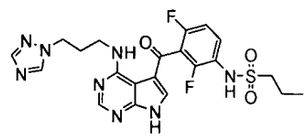
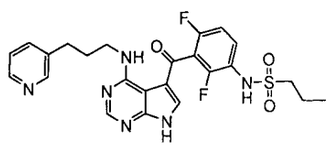
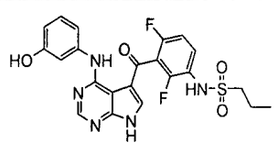
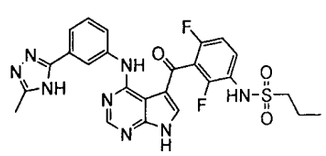
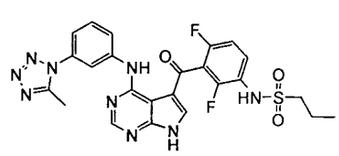
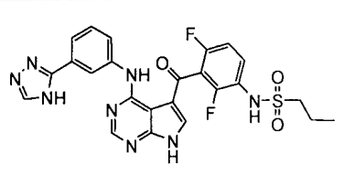
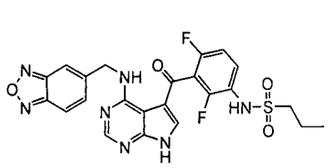
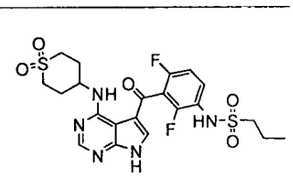
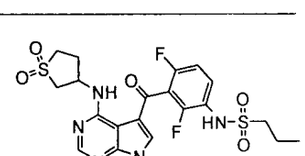
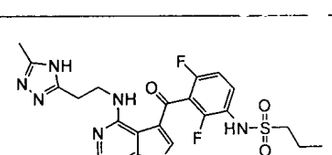
P-1108		4-Ciano-N-[2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-bencenosulfonamida	497.5
P-1109		ácido 2,2,2-trifluoro-etanosulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	478.0
P-1110		N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-difluorometoxi-bencenosulfonamida	538.5
P-1111		N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida	508.0
P-1112		N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,6-difluoro-bencenosulfonamida	508.0
P-1113		N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,4-difluoro-bencenosulfonamida	508.0
P-1114		Ácido propano-2-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	438.0
P-1115		N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-fluoro-bencenosulfonamida	490.5
P-1116		3-Ciano-N-[2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-bencenosulfonamida	497.5
P-1117		N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-fluoro-4-metoxi-bencenosulfonamida	520.5
P-1118		ácido 3,3,3-Trifluoro-propano-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	492.0
P-1119		N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-	538.5

		difluorometoxi-bencenosulfonamida	
P-1120		ácido 1-Etil-1H-pirazol-4-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	490.5
P-1121		ácido 1-Metil-1H-pirazol-4-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	476.0
P-1122		Ácido Piperidin-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	479.0
P-1123		Ácido ciclohexanosulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	478.0
P-1124		Ácido ciclopentanosulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	464.0
P-1125		Ácido pirrolidin-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	465.0
P-1126		ácido 2-Metil-propano-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	452.0
P-1127		Ácido dietilamin-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	467.5
P-1128		Ácido ciclobutanosulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	450.0
P-1129		Ácido morfolin-4-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	481.0
P-1130		ácido 6-Metoxi-piridin-3-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	503.0

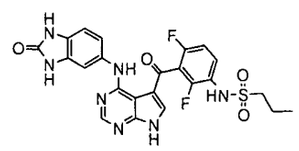
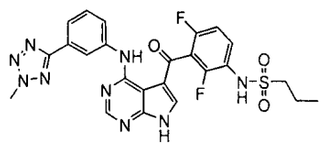
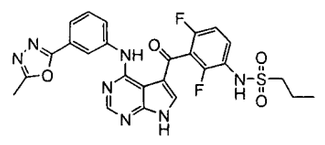
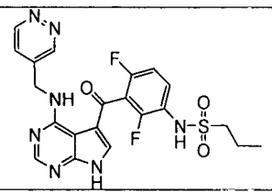
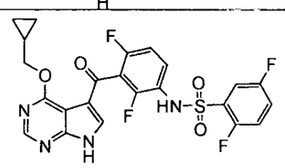
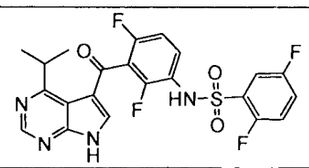
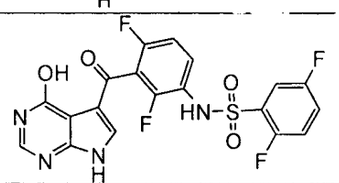
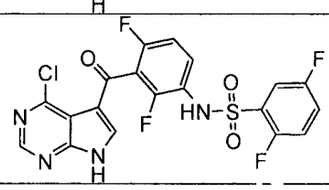
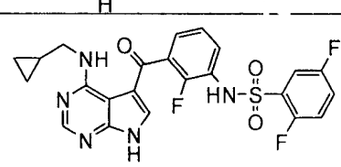
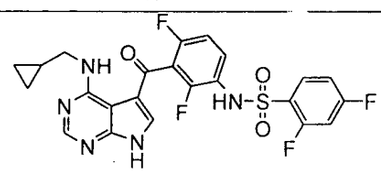
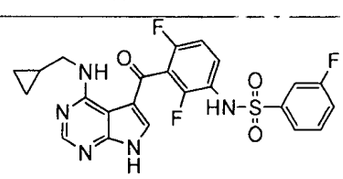
P-1131		ácido 6-metil-piridin-2-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	487.5
P-1132		Ácido piridin-3-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	473.0
P-1133		Ácido piridin-2-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	473.0
P-1134		Ácido propano-1-sulfónico {3-[4-(benzo[1,2,5]tiadiazol-5-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	530.0
P-1135		N-[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida	556.0
P-1136		N-{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida	543.5
P-1137		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida	520.5
P-1138		N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida	494.0
P-1139		N-{2,4-Difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida	572.0
P-1140		N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida	522.0
P-1141		N-[2,4-Difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida	556.0
P-1142		N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida	560.0

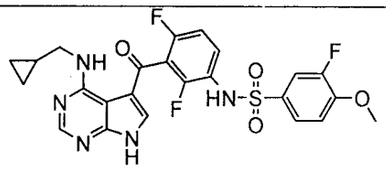
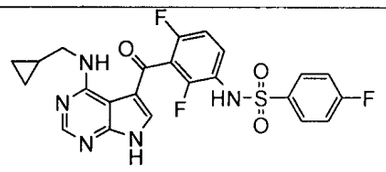
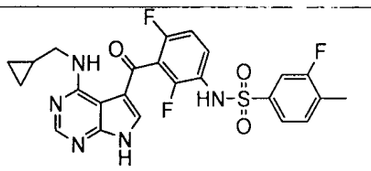
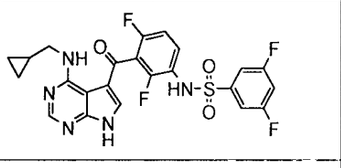
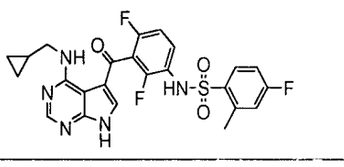
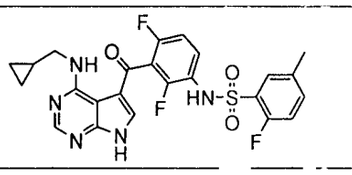
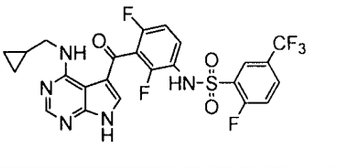
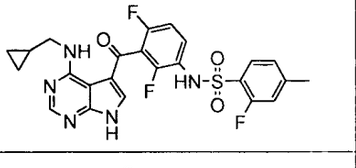
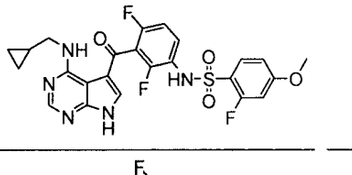
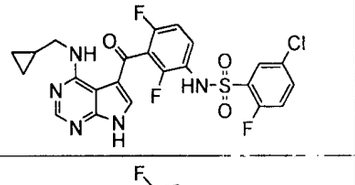
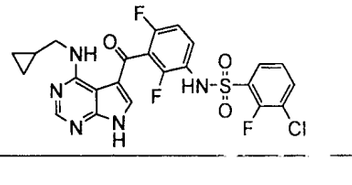
P-1143		N-{3-[4-(1,3-Dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida	560.0
P-1144		N-[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida	538.5
P-1145		N-{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida	525.5
P-1146		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida	502.0
P-1147		N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida	516.5
P-1148		N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida	476.0
P-1149		N-{2,4-Difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida	554.0
P-1150		N-{2,4-Difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida	506.0
P-1151		N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida	504.0
P-1152		N-[2,4-Difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida	538.5
P-1153		N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida	542.0
P-1154		N-{3-[4-(1,3-Dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida	542.0

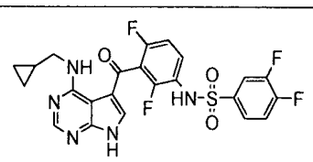
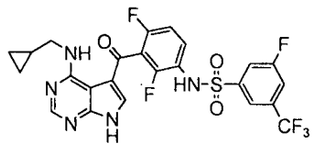
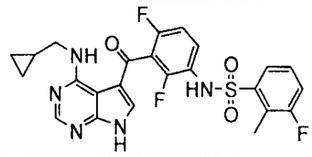
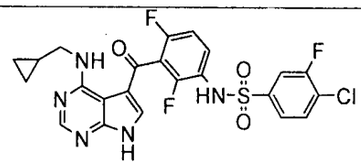
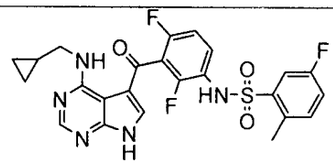
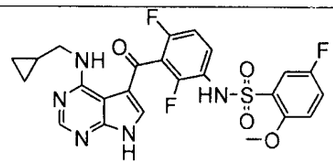
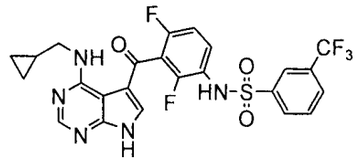
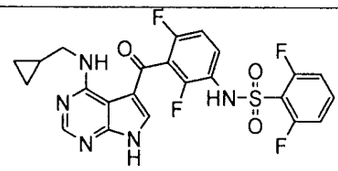
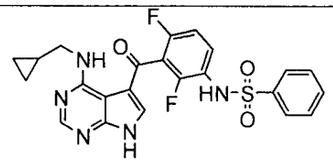
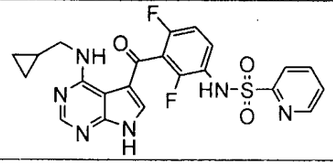
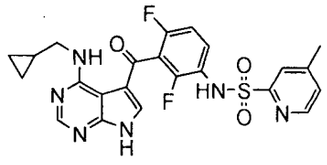
P-1155		N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-benceno sulfonamida	472.5
P-1156		Ácido dimetilamin-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida	439.0
P-1157		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1H-indazol-6-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	512.0
P-1158		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1H-indazol-5-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	512.0
P-1159		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(4-hidroxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	489.1
P-1160		Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[(5-metil-1H-pirazol-3-ilmetil)-amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida	488.0 $[M-H^+]^-$
P-1161		ácido 3-({5-[2,6-Difluoro-3-(propano-1-sulfonilamino)-benzoil]-7H-pirrolo[2,3-d]pirimidin-4-ilamino}-metil)-benzoico	530.0
P-1162		metil éster del ácido 4-{5-[2,6-Difluoro-3-(propano-1-sulfonilamino)-benzoil]-7H-pirrolo[2,3-d]pirimidin-4-ilamino}-benzoico	530.0
P-1163		ácido 4-{5-[2,6-Difluoro-3-(propano-1-sulfonilamino)-benzoil]-7H-pirrolo[2,3-d]pirimidin-4-ilamino}-benzoico	516.0
P-1164		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-[1,2,4]triazol-1-il-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	539.5
P-1165		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-oxazol-5-il-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	539.5
P-1166		Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[(piridin-3-ilmetil)-amino]-7H-pirrolo[2,3-d]pirimidin-5-	487.5

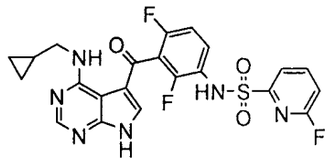
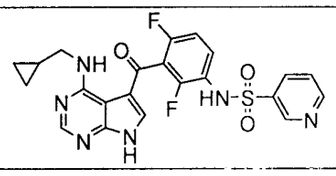
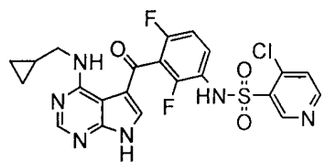
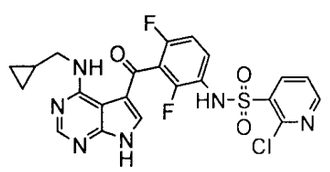
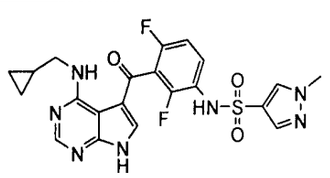
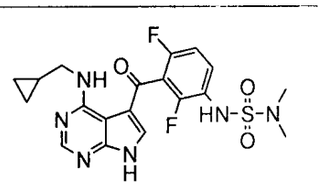
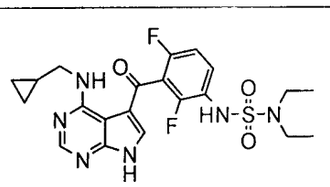
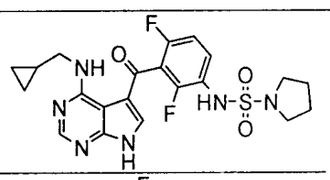
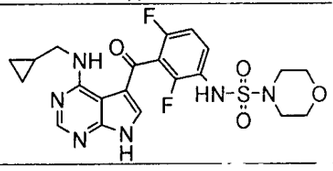
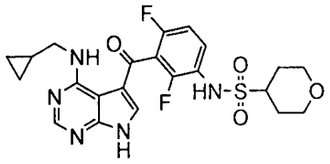
		carbonil}-fenil)-amida	
P-1167		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-[1,2,4]triazol-1-il-propilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	505.0
P-1168		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-piridin-3-il-propilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	515.5
P-1169		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-hidroxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	488.0
P-1170		Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(5-metil-4H-[1,2,4]triazol-3-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida	553.5
P-1171		Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(5-metil-tetrazol-1-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida	554.0
P-1172		Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(4H-[1,2,4]triazol-3-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida	539.5
P-1173		Ácido propano-1-sulfónico (3-{4-[(benzo[1,2,5]oxadiazol-5-ilmetil)-amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-2,4-difluoro-fenil)-amida	528.0
P-1174		Ácido propano-1-sulfónico {3-[4-(1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	528.0
P-1175		Ácido propano-1-sulfónico {3-[4-(1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	514.5
P-1176		Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[2-(5-metil-4H-[1,2,4]triazol-3-il)-etilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida	505.0

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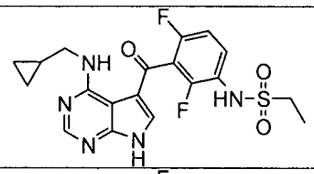
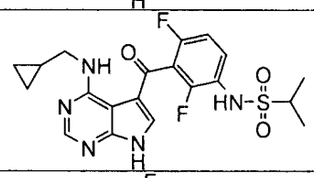
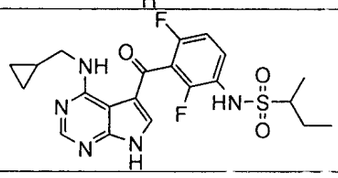
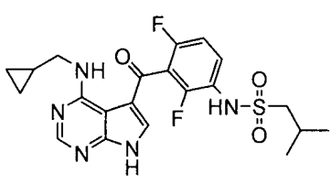
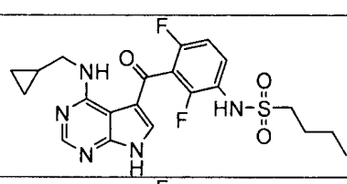
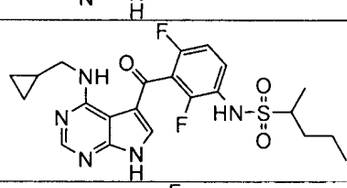
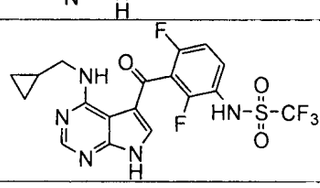
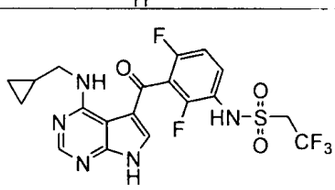
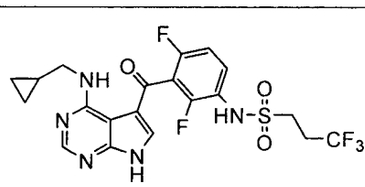
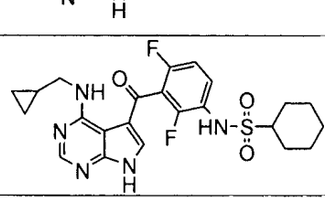
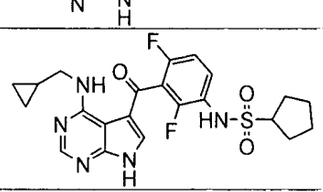
P-1177		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida	528.0
P-1178		Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(2-metil-2H-tetrazol-5-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida	554.0
P-1179		Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(5-metil-[1,3,4]oxadiazol-2-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida	554.0
P-1180		Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[(piridazin-4-ilmetil)-amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida	488.0
P-1181		N-[3-(4-Ciclopropilmetoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida	521.0
P-1182		N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida	493.0
P-1183		N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida	466.9
P-1184		N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida	
P-1185		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2-fluoro-fenil}-2,5-difluoro-bencenosulfonamida	502.0
P-1186		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,4-difluoro-bencenosulfonamida	520.5
P-1187		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-bencenosulfonamida	502.0

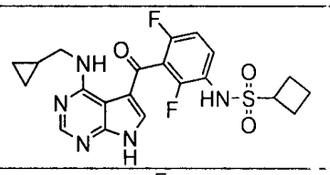
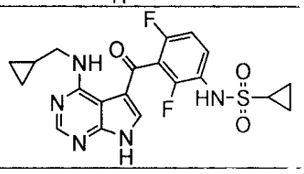
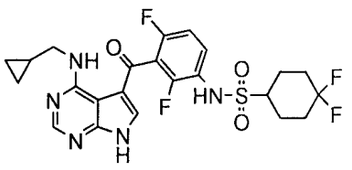
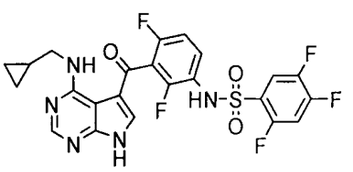
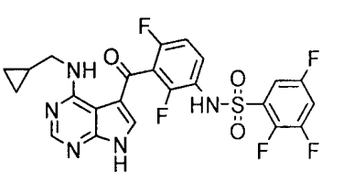
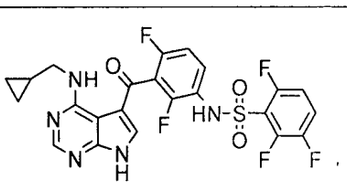
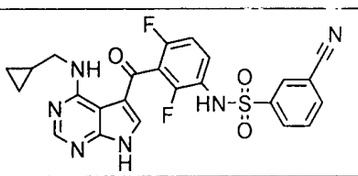
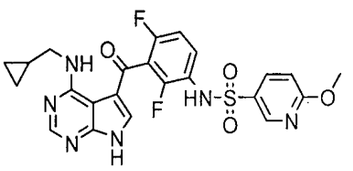
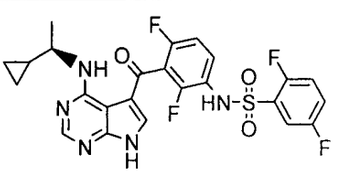
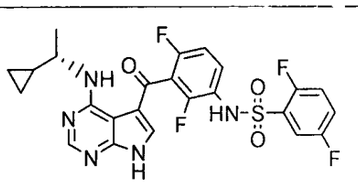
P-1188		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-4-metoxi-bencenosulfonamida	
P-1189		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-fluoro-bencenosulfonamida	502.0
P-1190		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-4-metil-bencenosulfonamida	516.5
P-1191		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3,5-difluoro-bencenosulfonamida	520.5
P-1192		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-fluoro-2-metil-bencenosulfonamida	516.5
P-1193		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-5-metil-bencenosulfonamida	516.5
P-1194		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-5-trifluorometil-bencenosulfonamida	570.5
P-1195		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-4-metil-bencenosulfonamida	516.5
P-1196		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-4-metoxi-bencenosulfonamida	532.0
P-1197		5-Cloro-N-{3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida	
P-1198		3-Cloro-N-{3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida	536.0

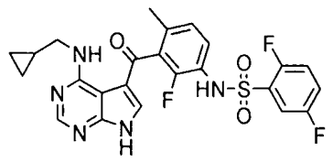
P-1199		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3,4-difluoro-bencenosulfonamida	520.5
P-1200		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-5-trifluorometil-bencenosulfonamida	570.5
P-1201		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-2-metil-bencenosulfonamida	516.5
P-1202		4-Cloro-N-{3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-bencenosulfonamida	536.0
P-1203		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-5-fluoro-2-metil-bencenosulfonamida	516.5
P-1204		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-5-fluoro-2-metoxi-bencenosulfonamida	532.0
P-1205		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-trifluorometil-bencenosulfonamida	552.5
P-1206		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,6-difluoro-bencenosulfonamida	520.5
P-1207		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-bencenosulfonamida	484.5
P-1208		Ácido piridin-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	485.5
P-1209		ácido 4-Metil-piridin-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	

P-1210		ácido 6-Fluoro-piridin-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	
P-1211		Ácido piridin-3-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	
P-1212		ácido 4-Cloro-piridin-3-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	
P-1213		ácido 2-Cloro-piridin-3-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	519.0
P-1214		ácido 1-Metil-1H-pirazol-4-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	488.5
P-1215		Ácido N,N-Dimetilamino-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	451.0
P-1216		Ácido N,N-Dietilamino-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	479.0
P-1217		Ácido pirrolidin-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	
P-1218		Ácido morfolin-4-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	493.5
P-1219		Ácido tetrahidro-piran-4-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	

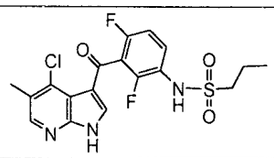
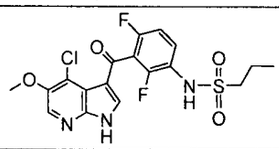
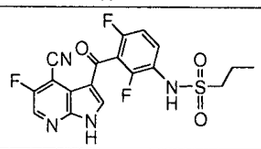
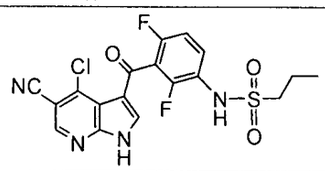
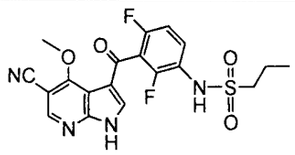
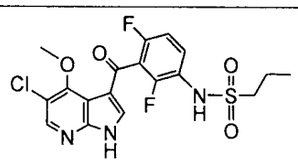
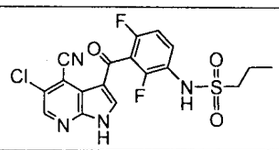
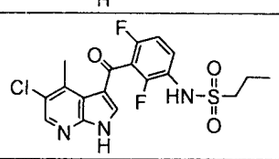
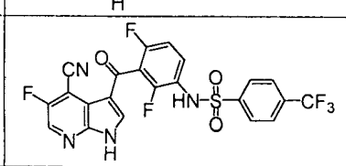
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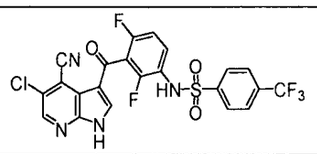
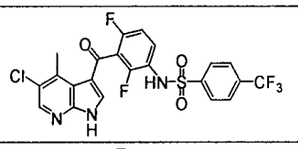
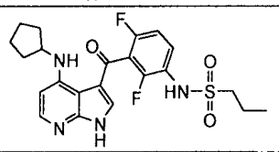
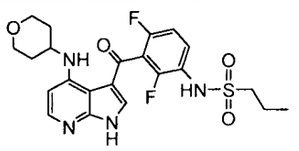
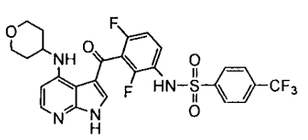
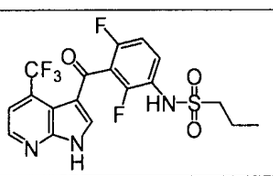
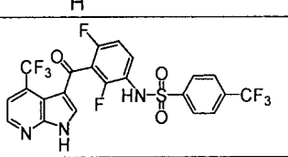
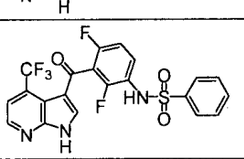
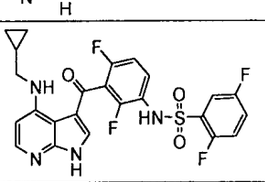
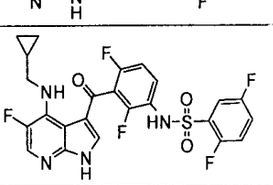
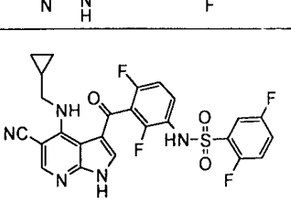
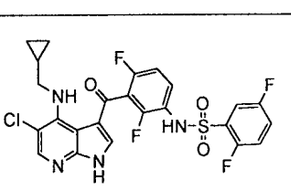
P-1220		Ácido etanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	
P-1221		Ácido propano-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	450.0
P-1222		Ácido butano-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	
P-1223		ácido 2-Metil-propano-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	464.0
P-1224		Ácido Butano-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	464.0
P-1225		Ácido Pentano-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	478.0
P-1226		N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-C,C,C-trifluoro-metanosulfonamida	
P-1227		ácido 2,2,2-trifluoro-etanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	490.0
P-1228		ácido 3,3,3-Trifluoro-propano-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	504.0
P-1229		Ácido ciclohexanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	490.5
P-1230		Ácido ciclopentanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	476.0

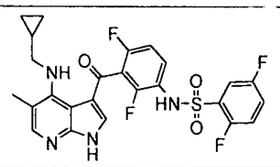
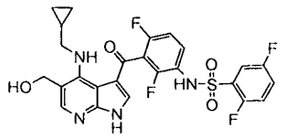
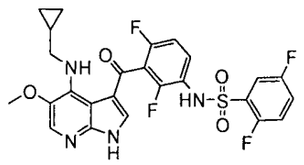
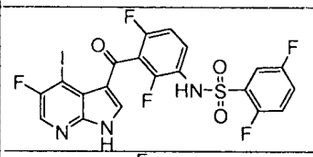
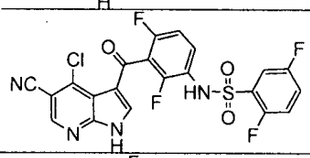
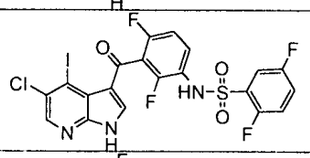
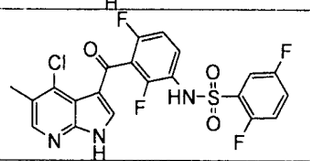
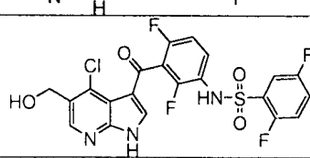
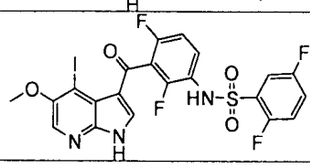
P-1231		Ácido ciclobutanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	462.5
P-1232		Ácido ciclopropanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	448.0
P-1233		ácido 4,4-Difluoro-ciclohexanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida	
P-1234		N-[3-[4-(ciclopropilmetilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil]-2,4,5-trifluoro-bencenosulfonamida	538.5
P-1235		N-[3-[4-(ciclopropilmetilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil]-2,3,5-trifluoro-bencenosulfonamida	538.5
P-1236		N-[3-[4-(ciclopropilmetilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil]-2,3,6-trifluoro-bencenosulfonamida	538.5
P-1237		3-ciano-N-[3-[4-(ciclopropilmetilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil]bencenosulfonamida	509.0
P-1238		N-[3-[4-(ciclopropilmetilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil]-6-metoxi-piridin-3-sulfonamida	
P-1239		N-[3-[4-[[(1R)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida	534.5
P-1240		N-[3-[4-[[(1S)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida	534.5

P-1241		N-[3-[4-(ciclopropilmetilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2-fluoro-4-metil-fenil]-2,5-difluoro-bencenosulfonamida	

[0054] En diversos aspectos y modalidades, se proporcionan los compuestos mostrados en la Tabla II a continuación, y/o sales farmacéuticamente aceptables de los compuestos mostrados en la Tabla II.

P-2001		[3-(4-Bromo-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida del ácido propano-1-sulfónico	427.9/ 429.9
P-2002		[3-Difluoro4-(-5-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-amida del ácido propano-1-sulfónico	443.9/ 446.1
P-2003		[3-Difluoro4-(-5-fluoro-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-amida del ácido propano-1-sulfónico	421.4
P-2004		[3-(4-Bromo-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida del ácido propano-1-sulfónico	439.1
P-2005		Ácido propano-1-sulfónico [3-(5-ciano-4-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida	435.1
P-2006		Ácido propano-1-sulfónico [3-(5-cloro-4-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida	444.1
P-2007		[3-(5-Bromo-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida del ácido propano-1-sulfónico	437.4/ 439.5
P-2008		[3-(5-Bromo-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida del ácido propano-1-sulfónico	428.1/ 430.1
P-2009		N-[3-(4-Etil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida	523.3

P-2010		N-[3-(5-Etil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida	539.3/ 541.3
P-2011		N-[3-(5-Etil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida	530.0/ 532.4
P-2012		[3-(4-Bromo-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida del ácido propano-1-sulfónico	463.8
P-2013		Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(tetrahidro-piran-4-ilamino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-fenil}-amida	479.1
P-2014		N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida	581.4
P-2015		[2,4-Difluoro-3-(4-fenil-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-amida del ácido propano-1-sulfónico	447.9
P-2016		N-[2,4-Difluoro-3-(1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida	549.9
P-2017		N-[2,4-Difluoro-3-(4-fluoro-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-bencenosulfonamida	481.9
P-2018		N-{3-[4-(Ciclopropilmetil-amino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida	519.1
P-2019		N-{3-[4-(Ciclopropilmetil-amino)-5-fluoro-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida	535.1
P-2020		N-{3-[5-Ciano-4-(ciclopropilmetil-amino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida	544.0
P-2021		N-{3-[5-Cloro-4-(ciclopropilmetil-amino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida	

P-2022		N-{3-[4-(Ciclopropilmetil-amino)-5-metil-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida	
P-2023		N-{3-[4-(Ciclopropilmetil-amino)-5-hidroximetil-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida	
P-2024		N-{3-[4-(Ciclopropilmetil-amino)-5-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida	
P-2025		N-[2,4-Difluoro-3-(5-fluoro-4-iodo-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida	593.8
P-2026		N-[3-(4-Cloro-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-2.5-difluoro-bencenosulfonamida	508.9/ 510.9
P-2027		N-[3-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-2.5-difluoro-bencenosulfonamida	
P-2028		N-[3-(4-Cloro-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-2.5-difluoro-bencenosulfonamida	
P-2029		N-[3-(4-Cloro-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-2.5-difluoro-bencenosulfonamida	
P-2030		N-[2,4-Difluoro-3-(4-iodo-5-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida	

[0055] En una modalidad de los compuestos contemplados en este documento, el compuesto se selecciona del grupo que consiste en:

N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1011**),

N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1013**),

N-[2,4-Difluoro-3-(4-morfolin-4-il-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1017**),

N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-

bencenosulfonamida (**P-1020**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1024**),
N-[2,4-Difluoro-3-(4-metilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1026**),
N-[3-(4-Amino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1031**),
N-[2,4-Difluoro-3-(4-propilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1032**),
N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1035**),
N-[2,4-Difluoro-3-(4-fenilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1037**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1039**),
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (**P-1040**),
Ácido propano-1-sulfónico [3-(4-ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1041**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida (**P-1042**),
N-{2,4-Difluoro-3-[4-(2-hidroxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1043**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida (**P-1044**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3,5-dimetil-bencenosulfonamida (**P-1045**),
N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-propil-bencenosulfonamida (**P-1046**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1047**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-fenilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1048**),
N-[3-(4-Dimetilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1049**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1050**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1051**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida (**P-1052**),

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N-{2,4-Difluoro-3-[4-(tetrahidro-furan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1054**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida (**P-1055**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-propil-bencenosulfonamida (**P-1056**),
N-{2,4-Difluoro-3-[4-(1-metil-piperidin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1057**),
N-{2,4-Difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1058**),
N-{3-[4-(2-Dimetilamino-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida (**P-1059**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1060**),
N-[2,4-Difluoro-3-(4-pirrolidin-1-il-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1061**),
N-{2,4-Difluoro-3-[4-(1-metil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1062**),
N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida (**P-1063**),
N-[2,4-Difluoro-3-(4-hidroxiamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1064**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(4-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1065**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-hidrazino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1066**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(naftalen-2-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1067**),
Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[(oxetan-3-ilmetil)-amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida (**P-1068**),
N-{2,4-Difluoro-3-[4-(4-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1069**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(naftalen-1-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1072**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1073**),
Ácido propano-1-sulfónico [3-(4-bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1074**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-propilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1075**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(piridin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-

fenil}-amida (**P-1076**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(piridin-2-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1077**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1078**),
Ácido propano-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1079**),
Ácido propano-1-sulfónico {3-[4-(1-benzil-pirrolidin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1080**),
Ácido propano-1-sulfónico [3-(4-ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1081**),
Ácido propano-1-sulfónico [3-(4-etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1082**),
Ácido propano-1-sulfónico {3-[4-(3-dimetilamino-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1083**),
{3-[4-(3-cloro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida del ácido propano-1-sulfónico (**P-1084**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1085**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1086**),
Ácido propano-1-sulfónico {3-[4-(4-cloro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1087**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1088**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(4-trifluorometil-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1089**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(6-metoxi-piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1090**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-trifluorometil-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1091**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1092**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-p-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1093**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1094**),
Ácido propano-1-sulfónico {3-[4-(1-etil-piperidin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1095**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1-metanosulfonil-piperidin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1096**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(tetrahidro-furan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1097**),

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-metilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1098**),

Ácido propano-1-sulfónico {3-[4-(1-etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1099**),

Ácido propano-1-sulfónico {3-[4-(1,3-dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1100**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(2-fluoro-4-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1101**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1-metil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1102**),

N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1103**),

N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1104**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-fluoro-5-metoxi-piridin-2-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1105**),

Ácido propano-1-sulfónico [2-fluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1106**),

4-Ciano-N-[2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-bencenosulfonamida (**P-1108**),

ácido 2,2,2-trifluoro-etanosulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1109**),

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-difluorometoxi-bencenosulfonamida (**P-1110**),

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1111**),

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,6-difluoro-bencenosulfonamida (**P-1112**),

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,4-difluoro-bencenosulfonamida (**P-1113**),

Ácido propano-2-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1114**),

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-fluoro-bencenosulfonamida (**P-1115**),

3-Ciano-N-[2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-bencenosulfonamida (**P-1116**),

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-fluoro-4-metoxi-bencenosulfonamida (**P-1117**),

ácido 3,3,3-Trifluoro-propano-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-

5-carbonil)-fenil]-amida (**P-1118**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-difluorometoxi-bencenosulfonamida (**P-1119**),
ácido 1-Etil-1H-pirazol-4-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1120**),
ácido 1-Metil-1H-pirazol-4-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1121**),
Ácido Piperidin-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1122**),
Ácido ciclohexanosulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1123**),
Ácido ciclopentanosulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1124**),
Ácido pirrolidin-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1125**),
ácido 2-Metil-propano-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1126**),
Ácido dietilamin-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1127**),
Ácido ciclobutanosulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1128**),
Ácido morfolin-4-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1129**),
ácido 6-Metoxi-piridin-3-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1130**),
ácido 6-metil-piridin-2-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1131**),
Ácido piridin-3-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1132**),
Ácido piridin-2-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1133**),
Ácido propano-1-sulfónico {3-[4-(benzo[1,2,5]tiadiazol-5-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1134**),
N-[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1135**),
N-{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1136**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1137**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1138**),

N-{2,4-Difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1139**),
N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1140**),
N-[2,4-Difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1141**),
N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1142**),
N-{3-[4-(1,3-Dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1143**),
N-[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1144**),
N-{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida (**P-1145**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1146**),
N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1147**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1148**),
N-{2,4-Difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida (**P-1149**),
N-{2,4-Difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida (**P-1150**),
N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1151**),
N-[2,4-Difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1152**),
N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1153**),
N-{3-[4-(1,3-Dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1154**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-bencenosulfonamida (**P-1155**),
Ácido dimetilamin-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1156**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1H-indazol-6-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1157**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1H-indazol-5-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1158**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(4-hidroxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-

carbonil]-fenil}-amida (**P-1159**),
Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[(5-metil-1H-pirazol-3-ilmetil)-amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida (**P-1160**),
ácido 3-({5-[2,6-Difluoro-3-(propano-1-sulfonilamino)-benzoil]-7H-pirrolo[2,3-d]pirimidin-4-ilamino}-metil)-benzoico (**P-1161**),
metil éster del ácido 4-{5-[2,6-Difluoro-3-(propano-1-sulfonilamino)-benzoil]-7H-pirrolo[2,3-d]pirimidin-4-ilamino}-benzoico (**P-1162**),
ácido 4-{5-[2,6-Difluoro-3-(propano-1-sulfonilamino)-benzoil]-7H-pirrolo[2,3-d]pirimidin-4-ilamino}-benzoico (**P-1163**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-[1,2,4]triazol-1-il-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1164**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-oxazol-5-il-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1165**),
Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[(piridin-3-ilmetil)-amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida (**P-1166**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-[1,2,4]triazol-1-il-propilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1167**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-piridin-3-il-propilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1168**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-hidroxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1169**),
Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(5-metil-4H-[1,2,4]triazol-3-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida (**P-1170**),
Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(5-metil-tetrazol-1-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida (**P-1171**),
Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(4H-[1,2,4]triazol-3-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida (**P-1172**),
Ácido propano-1-sulfónico (3-{4-[(benzo[1,2,5]oxadiazol-5-ilmetil)-amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-2,4-difluoro-fenil)-amida (**P-1173**),
Ácido propano-1-sulfónico {3-[4-(1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1174**),
Ácido propano-1-sulfónico {3-[4-(1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1175**),
Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[2-(5-metil-4H-[1,2,4]triazol-3-il)-etilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida (**P-1176**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1177**),
Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(2-metil-2H-tetrazol-5-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida (**P-1178**),
Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(5-metil-[1,3,4]oxadiazol-2-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida (**P-1179**),

Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[(piridazin-4-ilmetil)-amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida (**P-1180**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2-fluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1185**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,4-difluoro-bencenosulfonamida (**P-1186**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-bencenosulfonamida (**P-1187**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-4-metoxi-bencenosulfonamida (**P-1188**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-fluoro-bencenosulfonamida (**P-1189**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-4-metil-bencenosulfonamida (**P-1190**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3,5-difluoro-bencenosulfonamida (**P-1191**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-fluoro-2-metil-bencenosulfonamida (**P-1192**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-5-metil-bencenosulfonamida (**P-1193**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-5-trifluorometil-bencenosulfonamida (**P-1194**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-4-metil-bencenosulfonamida (**P-1195**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-4-metoxi-bencenosulfonamida (**P-1196**),
5-Cloro-N-{3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1197**),
3-Cloro-N-{3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1198**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3,4-difluoro-bencenosulfonamida (**P-1199**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-5-trifluorometil-bencenosulfonamida (**P-1200**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-2-metil-bencenosulfonamida (**P-1201**),
4-Cloro-N-{3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-bencenosulfonamida (**P-1202**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-5-fluoro-2-metil-bencenosulfonamida (**P-1203**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-5-fluoro-2-

metoxi-bencenosulfonamida (**P-1204**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-trifluorometil-bencenosulfonamida (**P-1205**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,6-difluoro-bencenosulfonamida (**P-1206**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-bencenosulfonamida (**P-1207**),
Ácido piridin-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1208**),
ácido 4-Metil-piridin-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1209**),
ácido 6-Fluoro-piridin-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1210**),
Ácido piridin-3-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1211**),
ácido 4-Cloro-piridin-3-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1212**),
ácido 2-Cloro-piridin-3-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1213**),
ácido 1-Metil-1H-pirazol-4-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1214**),
Ácido N,N-Dimetilamino-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1215**),
Ácido N,N-Dietilamino-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1216**),
Ácido pirrolidin-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1217**),
Ácido morfolin-4-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1218**),
Ácido tetrahidro-piran-4-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1219**),
Ácido etanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1220**),
Ácido propano-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1221**),
Ácido butano-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1222**),
ácido 2-Metil-propano-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1223**),
Ácido Butano-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1224**),

Ácido Pentano-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1225**),

N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-C,C,C-trifluoro-metanosulfonamida (**P-1226**),

ácido 2,2,2-trifluoro-etanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1227**),

ácido 3,3,3-Trifluoro-propano-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1228**),

Ácido ciclohexanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1229**),

Ácido ciclopentanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1230**),

Ácido ciclobutanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1231**),

Ácido ciclopropanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1232**),

ácido 4,4-Difluoro-ciclohexanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1233**),

3,3-Difluoro-ácido ciclopentanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1234**),

3-Fluoro-ácido ciclopentanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1235**),

Ácido propano-1-sulfónico [3-(4-ciclopentilamino-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2012**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(tetrahidro-piran-4-ilamino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-fenil}-amida (**P-2013**),

N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-2014**),

N-{3-[4-(Ciclopropilmetil-amino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-2018**),

N-{3-[4-(Ciclopropilmetil-amino)-5-fluoro-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-2019**),

N-{3-[5-Ciano-4-(ciclopropilmetil-amino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-2020**),

N-{3-[5-Cloro-4-(ciclopropilmetil-amino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-2021**),

N-{3-[4-(Ciclopropilmetil-amino)-5-metil-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-2022**),

N-{3-[4-(Ciclopropilmetil-amino)-5-hidroximetil-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-2023**),

N-{3-[4-(Ciclopropilmetil-amino)-5-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-2024**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0056] En una modalidad de los compuestos contemplados en este documento, el compuesto se selecciona del grupo que consiste en:
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1011**),
N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1013**),
N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1020**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1024**),
N-[2,4-Difluoro-3-(4-metilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1026**),
N-[3-(4-Amino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1031**),
N-[2,4-Difluoro-3-(4-propilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1032**),
N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1035**),
N-[2,4-Difluoro-3-(4-fenilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1037**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1039**),
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (**P-1040**),
Ácido propano-1-sulfónico [3-(4-ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1041**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida (**P-1042**),
N-{2,4-Difluoro-3-[4-(2-hidroxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1043**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida (**P-1044**),
N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-propil-bencenosulfonamida (**P-1046**),
N-[3-(4-Dimetilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1049**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-

bencenosulfonamida (**P-1050**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida (**P-1052**),
N-{2,4-Difluoro-3-[4-(tetrahidro-furan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1054**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida (**P-1055**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-propil-bencenosulfonamida (**P-1056**),
N-{2,4-Difluoro-3-[4-(1-metil-piperidin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1057**),
N-{2,4-Difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1058**),
N-{3-[4-(2-Dimetilamino-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida (**P-1059**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1060**),
N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-2014**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0057] En una modalidad de los compuestos contemplados en este documento, el compuesto se selecciona del grupo que consiste en:
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1011**),
N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1013**),
N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1020**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1024**),
N-[2,4-Difluoro-3-(4-metilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1026**),
N-[3-(4-Amino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1031**),
N-[2,4-Difluoro-3-(4-propilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1032**),
N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1035**),
N-[2,4-Difluoro-3-(4-fenilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1037**),

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1039**),
N-{2,4-Difluoro-3-[4-(2-hidroxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1043**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida (**P-1044**),
N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-propil-bencenosulfonamida (**P-1046**),
N-[3-(4-Dimetilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1049**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1050**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida (**P-1052**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-propil-bencenosulfonamida (**P-1056**),
N-{2,4-Difluoro-3-[4-(1-metil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1062**),
N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida (**P-1063**),
4-Ciano-N-[2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-bencenosulfonamida (**P-1108**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-difluorometoxi-bencenosulfonamida (**P-1110**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-difluorometoxi-bencenosulfonamida (**P-1119**),
ácido 1-Metil-1H-pirazol-4-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1121**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[**0058**] En una modalidad de los compuestos contemplados en este documento, el compuesto se selecciona del grupo que consiste en:
Ácido propano-1-sulfónico [3-(4-ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1041**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1060**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(4-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1065**),
N-{2,4-Difluoro-3-[4-(4-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1069**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(naftalen-1-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-

carbonil]-fenil}-amida (**P-1072**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1073**),
Ácido propano-1-sulfónico [3-(4-bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1074**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-propilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1075**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(piridin-2-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1077**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1078**),
Ácido propano-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1079**),
Ácido propano-1-sulfónico [3-(4-ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1081**),
Ácido propano-1-sulfónico [3-(4-etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1082**),
Ácido propano-1-sulfónico {3-[4-(3-dimetilamino-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1083**),
{3-[4-(3-cloro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida del ácido propano-1-sulfónico (**P-1084**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1085**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1086**),
Ácido propano-1-sulfónico {3-[4-(4-cloro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1087**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1088**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(4-trifluorometil-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1089**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(6-metoxi-piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1090**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-trifluorometil-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1091**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1092**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-p-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1093**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1094**),

Ácido propano-1-sulfónico {3-[4-(1-etil-piperidin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1095**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1-metanosulfonil-piperidin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1096**),
Ácido propano-1-sulfónico {3-[4-(1-etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1099**),
Ácido propano-1-sulfónico {3-[4-(1,3-dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1100**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(2-fluoro-4-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1101**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1-metil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1102**),
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1103**),
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1104**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-fluoro-5-metoxi-piridin-2-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1105**),
N-[3-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1107**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1111**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-fluoro-bencenosulfonamida (**P-1115**),
Ácido Piperidin-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1122**),
ácido 2-Metil-propano-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1126**),
Ácido piridin-3-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1132**),
Ácido propano-1-sulfónico {3-[4-(benzo[1,2,5]tiadiazol-5-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1134**),
N-[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1135**),
N-{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1136**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1137**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1138**),
N-{2,4-Difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-

bencenosulfonamida (**P-1139**),
N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1140**),
N-[2,4-Difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1141**),
N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1142**),
N-{3-[4-(1,3-Dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1143**),
N-[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1144**),
N-{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida (**P-1145**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1146**),
N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1147**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1148**),
N-{2,4-Difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida (**P-1149**),
N-{2,4-Difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida (**P-1150**),
N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1151**),
N-[2,4-Difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1152**),
N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1153**),
N-{3-[4-(1,3-Dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1154**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1H-indazol-6-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1157**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1H-indazol-5-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1158**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(4-hidroxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1159**),
metil éster del ácido 4-{5-[2,6-Difluoro-3-(propano-1-sulfonilamino)-benzoil]-7H-pirrolo[2,3-d]pirimidin-4-ilamino}-benzoico (**P-1162**),
Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(5-metil-tetrazol-1-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida (**P-1171**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1177**),
Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(5-metil-[1,3,4]oxadiazol-2-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida (**P-1179**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0059] En una modalidad de los compuestos contemplados en este documento, el compuesto se selecciona del grupo que consiste en:
N-{2,4-Difluoro-3-[4-(4-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1069**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1073**),
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1103**),
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1104**),
N-[3-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1107**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1111**),
N-[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1135**),
N-{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1136**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1137**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1138**),
N-{2,4-Difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1139**),
N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1140**),
N-[2,4-Difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1141**),
N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1142**),
N-{3-[4-(1,3-Dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1143**),
N-[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1144**),
N-{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-

bencenosulfonamida (**P-1145**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1146**),
N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1147**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1148**),
N-{2,4-Difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida (**P-1149**),
N-{2,4-Difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida (**P-1150**),
N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1151**),
N-[2,4-Difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1152**),
N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1153**),
N-{3-[4-(1,3-Dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1154**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0060] En una modalidad de los compuestos contemplados en este documento, el compuesto se selecciona del grupo que consiste en:
N-{2,4-Difluoro-3-[4-(4-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1069**),
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1104**),
N-[3-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1107**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1111**),
N-[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1135**),
N-{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1136**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1137**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1138**),
N-{2,4-Difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1139**),

N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1140**),
N-[2,4-Difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1141**),
N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1142**),
N-{3-[4-(1,3-Dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1143**), y

cualquier sal, profármaco, tautómero, o estereoisómero de los mismos.

[0061] En una modalidad de los compuestos contemplados en este documento, el compuesto se selecciona del grupo que consiste en:
Ácido propano-1-sulfónico [3-(4-cloro-5-metil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2001**),
Ácido propano-1-sulfónico [3-(4-cloro-5-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2002**),
Ácido propano-1-sulfónico [3-(4-ciano-5-fluoro-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2003**),
Ácido propano-1-sulfónico [3-(4-cloro-5-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2004**),
Ácido propano-1-sulfónico [3-(5-ciano-4-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2005**),
Ácido propano-1-sulfónico [3-(5-cloro-4-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2006**),
Ácido propano-1-sulfónico [3-(5-cloro-4-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2007**),
Ácido propano-1-sulfónico [3-(5-cloro-4-metil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2008**),
N-[3-(4-Ciano-5-fluoro-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-2009**),
N-[3-(5-Cloro-4-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-2010**),
N-[3-(5-Cloro-4-metil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-2011**),
N-[2,4-Difluoro-3-(5-fluoro-4-iodo-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-2025**),
N-[3-(4-Cloro-5-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-2026**),
N-[3-(5-Cloro-4-iodo-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-2027**),
N-[3-(4-Cloro-5-metil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-

bencenosulfonamida (**P-2028**),
N-[3-(4-Cloro-5-hidroximetil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-2029**),
N-[2,4-Difluoro-3-(4-iodo-5-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-2030**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0062] En un cuarto aspecto, se proporcionan compuestos en donde el compuesto se selecciona del grupo que consiste en:
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1001**),
Ácido propano-1-sulfónico [3-(4-etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1002**),
ácido 2-Metil-propano-1-sulfónico [2,4-difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1003**),
ácido 2-Metil-propano-1-sulfónico [2,4-difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1004**),
N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida (**P-1005**),
N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1006**),
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida (**P-1007**),
N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida (**P-1008**),
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida (**P-1009**),
N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida (**P-1010**),
N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1012**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-isobutil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1014**),
N-[2,4-Difluoro-3-(4-isobutil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1015**),
N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1016**),
ácido 6-Metoxi-piridin-3-sulfónico [2,4-difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1018**),
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida (**P-1019**),

N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-iloxi)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1021**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1022**),
N-[3-(4-Ciano-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1023**),
N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3,5-dimetil-bencenosulfonamida (**P-1025**),
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3,5-dimetil-bencenosulfonamida (**P-1027**),
N-[2,4-Difluoro-3-(4-isobutoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1028**),
N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1029**),
N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida (**P-1030**),
Ácido propano-1-sulfónico [3-(4-cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1033**),
N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (**P-1034**),
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-fluoro-4-metoxi-bencenosulfonamida (**P-1036**),
N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (**P-1038**),
N-[3-(4-Ciclopropilmetoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1053**),
N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1070**),
N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1071**),
N-[3-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1107**),
N-[3-(4-Ciclopropilmetoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1181**),
N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1182**),
N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1183**),
N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1184**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-

amida (**P-2015**),
N-[2,4-Difluoro-3-(4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-2016**),
N-[2,4-Difluoro-3-(4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-bencenosulfonamida (**P-2017**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0063] En una modalidad del cuarto aspecto, el compuesto se selecciona del grupo que consiste en:
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1001**),
N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida (**P-1005**),
N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1006**),
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida (**P-1007**),
N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1012**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-isobutil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1014**),
N-[2,4-Difluoro-3-(4-isobutil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1015**),
N-[2,4-Difluoro-3-(4-isobutoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1028**),
N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1029**),
N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (**P-1034**),
N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (**P-1038**),
N-[3-(4-Ciclopropilmetoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1053**),
N-[2,4-Difluoro-3-(4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-2016**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0064] En una modalidad del cuarto aspecto, el compuesto se selecciona del grupo que consiste en:
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1001**),
N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida

(**P-1005**),
N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1006**),
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida (**P-1007**),
N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1012**),
N-[2,4-Difluoro-3-(4-isobutoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1028**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0065] En una modalidad del cuarto aspecto, el compuesto se selecciona del grupo que consiste en:
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida (**P-1009**),
N-[2,4-Difluoro-3-(4-isobutil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1015**),
N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1016**),
N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-iloxi)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1021**),
N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1029**),
Ácido propano-1-sulfónico [3-(4-cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1033**),
N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (**P-1038**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0066] En una modalidad del cuarto aspecto, el compuesto se selecciona del grupo que consiste en:
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1022**),
N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1070**),
N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1071**),
N-[3-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1107**),
N-[3-(4-Ciclopropilmetoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1181**),

N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1182**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0067] En una modalidad de cualquiera de los aspectos y modalidades anteriores, el compuesto incluye cualquier profármaco del mismo.

[0068] En una modalidad de cualquiera de los aspectos y modalidades anteriores, el compuesto incluye cualquier tautómero del mismo.

[0069] En una modalidad de cualquiera de los aspectos y modalidades anteriores, el compuesto incluye cualquier estereoisómero del mismo.

[0070] En una modalidad de cualquiera de los aspectos y modalidades anteriores, el compuesto incluye cualquier formulación farmacéuticamente aceptable del mismo.

[0071] En una modalidad de cualquiera de los aspectos y modalidades anteriores, el compuesto incluye cualquier conjugado del mismo.

[0072] En una modalidad de cualquiera de los aspectos y modalidades anteriores, el compuesto incluye cualquier derivado del mismo.

[0073] En una modalidad de cualquiera de los aspectos y modalidades anteriores, el compuesto incluye cualquier forma del mismo.

[0074] Con respecto a los compuestos descritos en este documento, a menos que se indique claramente lo contrario, la especificación de un compuesto o grupo de compuestos incluye sales de tales compuestos (incluyendo sales farmacéuticamente aceptables), formulaciones de tales compuestos (incluyendo formulaciones farmacéuticamente aceptables), conjugados de los mismos, derivados de los mismos, formas de los mismos, profármacos de los mismos, y todos los estereoisómeros de los mismos. En referencia a las composiciones, kits, métodos de uso, etc. de los compuestos como se describe en este documento, es decir, compuestos de la invención, se entiende (a menos que se indique de otra manera) que un compuesto como se describe en este documento incluye compuestos de la Fórmula I incluyendo todas las sub-modalidades de los mismos, compuestos de la Fórmula II incluyendo todas las sub-modalidades de los mismos, y compuestos como se listan en el tercer aspecto anterior, incluyendo todas las sub-modalidades de los mismos.

[0075] En un quinto aspecto, se proporcionan métodos para tratar cualquier enfermedad o padecimiento mediado por la proteína cinasa Raf en un sujeto animal en necesidad de ello, en donde el método implica administrar al sujeto una cantidad efectiva de uno cualquiera o más compuestos como se describe en este documento. En ciertas modalidades, el método implica administrar al sujeto una cantidad efectiva de uno cualquiera o más compuestos como se describe en este documento en combinación con una o más de otras terapias para la enfermedad o padecimiento.

[0076] En un sexto aspecto, se proporcionan métodos para tratar cualquier enfermedad o padecimiento mediado por la proteína cinasa B-Raf, incluyendo cualquier enfermedad o padecimiento mediado por la cinasa mutante de B-Raf, en un sujeto animal en necesidad de ello, en donde el método implica administrar al sujeto una cantidad efectiva de uno cualquiera o más compuestos como se describe en este documento. En ciertas modalidades, el método implica administrar al sujeto una cantidad efectiva de uno cualquiera o más compuestos como se describe en este documento en combinación con una o más de otras terapias para la enfermedad o padecimiento.

[0077] En un séptimo aspecto, se proporcionan métodos para tratar cualquier enfermedad o padecimiento mediado por la proteína cinasa mutante B-Raf V600E en un sujeto animal en necesidad de ello, en donde el método implica administrar al sujeto una cantidad efectiva de uno cualquiera o más compuestos como se describe en este documento. En ciertas modalidades, el método implica administrar al sujeto una cantidad efectiva de uno cualquiera o más compuestos como se describe en este documento en combinación con una o más de otras terapias para la enfermedad o padecimiento.

[0078] En un octavo aspecto, se proporcionan métodos para tratar cualquier enfermedad o padecimiento mediado por la proteína cinasa c-Raf-1, incluyendo cualquier enfermedad o padecimiento mediado por la cinasa mutante de c-Raf-1, en un sujeto animal en necesidad de ello, en donde el método implica administrar al sujeto una cantidad efectiva de uno cualquiera o más compuestos como se describe en este documento. En ciertas modalidades, el método implica administrar al sujeto una cantidad efectiva de uno cualquiera o más compuestos como se describe en este documento en combinación con una o más de otras terapias para la enfermedad o padecimiento.

[0079] En un noveno aspecto, un compuesto como se describe en este documento es un inhibidor de Raf cinasa y tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa Raf. En algunas modalidades, un compuesto como se describe en este documento tendrá una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM con respecto a B-Raf, c-Raf-1, o mutante B-Raf V600E. En algunas modalidades, un compuesto como se describe en este documento inhibirá de manera selectiva una o más cinasas Raf en relación con una o más cinasas no Raf diferentes. En algunas modalidades, un compuesto como se describe en este documento inhibirá de manera selectiva una cinasa Raf en relación con una o más cinasas Raf diferentes. En algunas modalidades, el compuesto como se describe en este documento inhibirá de manera selectiva una mutación de la cinasa Raf en relación con la cinasa tipo silvestre, por ejemplo mutante B-Raf V600E en relación con B-Raf tipo silvestre.

[0080] En un décimo aspecto, un compuesto como se describe en este documento es un inhibidor de B-Raf V600E y tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa mutante B-Raf V600E. En algunas modalidades, el compuesto es selectivo en relación con otras proteína cinasas, de tal modo que la relación de IC_{50} para otra cinasa valorada de manera comparable, dividida entre la IC_{50} para la cinasa mutante B-Raf V600E es >10,

también >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, en donde la otra proteína cinasa incluye, pero no se limita a, CSK, cinasa del receptor de insulina, AMPK, PDGFR o VEGFR. En algunas modalidades, el compuesto también es selectivo en relación con una o más cinasas Raf diferentes de tal modo que la relación de IC_{50} para otra cinasa Raf valorada de manera comparable, dividida entre la IC_{50} para la cinasa mutante B-Raf V600E es >10, también >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100.

[0081] En un décimo primer aspecto, un compuesto como se describe en este documento es un inhibidor de c-Raf-1 y tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa c-Raf-1. En algunas modalidades, el compuesto es selectivo en relación con otras proteína cinasas, de tal modo que la relación de IC_{50} para otra cinasa valorada de manera comparable; dividida entre la IC_{50} para la c-Raf-1 es >10, también >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, en donde la otra proteína cinasa incluye, pero no se limita a, CSK, cinasa del receptor de insulina, AMPK, PDGFR o VEGFR. En algunas modalidades, el compuesto también es selectivo en relación con una o más cinasas Raf diferentes de tal modo que la relación de IC_{50} para otra cinasa Raf valorada de manera comparable, dividida entre la IC_{50} para la cinasa c-Raf-1 es >10, también >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. En algunas modalidades, un inhibidor de c-Raf-1 es selectivo en relación con por lo menos B-Raf y B-Raf V600E. En una modalidad, el inhibidor de c-Raf-1 es un compuesto seleccionado del grupo que consiste en:
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida (**P-1009**),
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1011**),
N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1013**),
N-[2,4-Difluoro-3-(4-isobutil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1015**),
N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1016**),
N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1020**),
N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-iloxi)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1021**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1024**),
N-[2,4-Difluoro-3-(4-metilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1026**),
N-[2,4-Difluoro-3-(4-isobutoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-

bencenosulfonamida (**P-1028**),
N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1029**),
N-[3-(4-Amino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1031**),
N-[2,4-Difluoro-3-(4-propilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1032**),
N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1035**),
N-[2,4-Difluoro-3-(4-fenilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1037**),
N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (**P-1038**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1039**),
N-{2,4-Difluoro-3-[4-(2-hidroxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1043**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida (**P-1044**),
N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-propil-bencenosulfonamida (**P-1046**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1047**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-fenilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1048**),
N-[3-(4-Dimetilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1049**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1050**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida (**P-1052**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-propil-bencenosulfonamida (**P-1056**),
N-{2,4-Difluoro-3-[4-(1-metil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1062**),
N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida (**P-1063**),
4-Ciano-N-[2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-bencenosulfonamida (**P-1108**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-difluorometoxi-bencenosulfonamida (**P-1110**),

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-difluorometoxi-bencenosulfonamida (**P-1119**),
ácido 1-Metil-1H-pirazol-4-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1121**),
N-[3-(4-Ciano-5-fluoro-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-2009**),
N-[3-(5-Cloro-4-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-2010**),
N-[2,4-Difluoro-3-(4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-bencenosulfonamida (**P-2017**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0082] En una modalidad, el inhibidor de c-Raf-1 es un compuesto seleccionado del grupo que consiste en:
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1011**),
N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1013**),
N-[2,4-Difluoro-3-(4-isobutil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1015**),
N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1020**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1024**),
N-[2,4-Difluoro-3-(4-metilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1026**),
N-[2,4-Difluoro-3-(4-isobutoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1028**),
N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1029**),
N-[3-(4-Amino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1031**),
N-[2,4-Difluoro-3-(4-propilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1032**),
N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1035**),
N-[2,4-Difluoro-3-(4-fenilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1037**),
N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (**P-1038**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-

bencenosulfonamida (**P-1039**),
N-{2,4-Difluoro-3-[4-(2-hidroxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1043**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida (**P-1044**),
N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-propil-bencenosulfonamida (**P-1046**),
N-[3-(4-Dimetilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1049**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1050**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida (**P-1052**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-propil-bencenosulfonamida (**P-1056**),
N-[3-(5-Cloro-4-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-2010**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0083] En una modalidad, el inhibidor de c-Raf-1 es un compuesto seleccionado del grupo que consiste en:
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1011**),
N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1013**),
N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1020**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1024**),
N-[2,4-Difluoro-3-(4-metilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1026**),
N-[2,4-Difluoro-3-(4-isobutoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1028**),
N-[3-(4-Amino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1031**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1039**), y

cualquier sal farmacéuticamente aceptable de los mismos.

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[0084] En un décimo segundo aspecto, un compuesto como se describe en este documento es un pan inhibidor de Raf , es decir, inhibe cada una de cinasa mutante B-Raf V600E, cinasa B-Raf y cinasa c-Raf-1, con una IC_{50} de menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en cada uno de un ensayo generalmente aceptado de actividad de cinasa mutante B-Raf V600E, ensayo de actividad de cinasa B-Raf, y ensayo de actividad de cinasa c-Raf-1. En algunas modalidades, los compuestos son efectivamente igual de potentes sobre cada una de B-Raf V600E, B-Raf y c-Raf-1, es decir, la relación de IC_{50} para cualquiera de B-Raf V600E, B-Raf y c-Raf-1 dividida entre la IC_{50} para cualquier otra de B-Raf V600E, B-Raf y c-Raf-1 (por ejemplo, IC_{50} de B-Raf dividida entre IC_{50} de B-Raf V600E) se encuentra en el intervalo de 10 a 0.1, también 5 a 0.2. En algunas modalidades, el compuesto es selectivo en relación con otras proteína cinasas, de tal modo que la relación de IC_{50} para otra cinasa valorada de manera comparable, dividida entre la IC_{50} para cualquiera de B-Raf V600E, B-Raf y c-Raf-1 es >10, también >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, en donde la otra proteína cinasa incluye, pero no se limita a, CSK, cinasa del receptor de insulina, AMPK, PDGFR o VEGFR. En una modalidad, el pan inhibidor de Raf es un compuesto seleccionado del grupo que consiste en:

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1022**),

N-[2,4-Difluoro-3-(4-propilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1032**),

N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1035**),

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1039**),

Ácido propano-1-sulfónico [3-(4-ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1041**),

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida (**P-1042**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1047**),

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-fenilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1048**),

N-{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1050**),

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1051**),

N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida (**P-1052**),

N-{2,4-Difluoro-3-[4-(tetrahidro-furan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1054**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1060**),

N-{2,4-Difluoro-3-[4-(1-metil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1062**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(4-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1065**),

N-{2,4-Difluoro-3-[4-(4-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1069**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(naftalen-1-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1072**),

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1073**),

Ácido propano-1-sulfónico [3-(4-bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1074**),

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-propilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1075**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(piridin-2-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1077**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1078**),

Ácido propano-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1079**),

Ácido propano-1-sulfónico [3-(4-ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1081**),

Ácido propano-1-sulfónico [3-(4-etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1082**),

Ácido propano-1-sulfónico {3-[4-(3-dimetilamino-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1083**),

{3-[4-(3-cloro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida del ácido propano-1-sulfónico (**P-1084**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1085**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1086**),

Ácido propano-1-sulfónico {3-[4-(4-cloro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1087**),

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1088**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(4-trifluorometil-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1089**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(6-metoxi-piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1090**),

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-trifluorometil-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-

carbonil]-fenil}-amida (**P-1091**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1092**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-p-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1093**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1094**),
Ácido propano-1-sulfónico {3-[4-(1-etil-piperidin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1095**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1-metanosulfonil-piperidin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1096**),
Ácido propano-1-sulfónico {3-[4-(1-etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1099**),
Ácido propano-1-sulfónico {3-[4-(1,3-dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1100**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(2-fluoro-4-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1101**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1-metil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1102**),
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1103**),
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1104**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-fluoro-5-metoxi-piridin-2-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1105**),
N-[3-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1107**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1111**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-fluoro-bencenosulfonamida (**P-1115**),
Ácido Piperidin-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1122**),
ácido 2-Metil-propano-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1126**),
Ácido piridin-3-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1132**),
Ácido propano-1-sulfónico {3-[4-(benzo[1,2,5]tiadiazol-5-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1134**),
N-[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1135**),

N-{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1136**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1137**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1138**),
N-{2,4-Difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1139**),
N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1140**),
N-[2,4-Difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1141**),
N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1142**),
N-{3-[4-(1,3-Dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1143**),
N-[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1144**),
N-{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida (**P-1145**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1146**),
N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1147**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1148**),
N-{2,4-Difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida (**P-1149**),
N-{2,4-Difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida (**P-1150**),
N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1151**),
N-[2,4-Difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1152**),
N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1153**),
N-{3-[4-(1,3-Dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1154**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1H-indazol-6-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1157**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1H-indazol-5-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-

carbonil]-fenil}-amida (**P-1158**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(4-hidroxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1159**),
metil éster del ácido 4-{5-[2,6-Difluoro-3-(propano-1-sulfonilamino)-benzoil]-7H-pirrolo[2,3-d]pirimidin-4-ilamino}-benzoico (**P-1162**),
Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(5-metil-tetrazol-1-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida (**P-1171**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1177**),
Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(5-metil-[1,3,4]oxadiazol-2-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida (**P-1179**),
N-[3-(4-Ciclopropilmetoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1181**),
N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1182**),
Ácido propano-1-sulfónico [3-(4-cloro-5-metil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2001**),
Ácido propano-1-sulfónico [3-(4-cloro-5-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2002**),
Ácido propano-1-sulfónico [3-(4-ciano-5-fluoro-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2003**),
Ácido propano-1-sulfónico [3-(4-cloro-5-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2004**),
Ácido propano-1-sulfónico [3-(5-ciano-4-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2005**),
Ácido propano-1-sulfónico [3-(5-cloro-4-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2006**),
Ácido propano-1-sulfónico [3-(5-cloro-4-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2007**),
Ácido propano-1-sulfónico [3-(5-cloro-4-metil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2008**),
N-[3-(4-Ciano-5-fluoro-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-2009**),
N-[3-(5-Cloro-4-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-2010**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(tetrahidro-piran-4-ilamino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-fenil}-amida (**P-2013**), y
cualquier sal farmacéuticamente aceptable de los mismos.

[0085] En una modalidad, el pan inhibidor de Raf es un compuesto seleccionado del grupo que consiste en:

Ácido propano-1-sulfónico [3-(4-ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1041**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida (**P-1042**),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1051**),
N-{2,4-Difluoro-3-[4-(tetrahidro-furan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1054**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1060**),
Ácido propano-1-sulfónico [3-(4-cloro-5-metil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2001**),
Ácido propano-1-sulfónico [3-(4-cloro-5-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2002**),
Ácido propano-1-sulfónico [3-(4-ciano-5-fluoro-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2003**),
Ácido propano-1-sulfónico [3-(4-cloro-5-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2004**),
Ácido propano-1-sulfónico [3-(5-ciano-4-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2005**),
Ácido propano-1-sulfónico [3-(5-cloro-4-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2006**),
Ácido propano-1-sulfónico [3-(5-cloro-4-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2007**),
Ácido propano-1-sulfónico [3-(5-cloro-4-metil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2008**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0086] En una modalidad, el pan inhibidor de Raf es un compuesto seleccionado del grupo que consiste en:
N-[2,4-Difluoro-3-(4-propilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1032**),
N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1035**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (**P-1039**),
Ácido propano-1-sulfónico [3-(4-ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1041**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida (**P-1042**),
N-{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-

bencenosulfonamida (**P-1050**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida (**P-1052**),
N-{2,4-Difluoro-3-[4-(tetrahidro-furan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (**P-1054**),
Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida (**P-1060**),
N-[3-(5-Cloro-4-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-2010**), y
cualquier sal farmacéuticamente aceptable de los mismos.

[0087] En una modalidad, el pan inhibidor de Raf es un compuesto seleccionado del grupo que consiste en:
Ácido propano-1-sulfónico [3-(4-ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (**P-1041**),
Ácido propano-1-sulfónico [3-(4-cloro-5-metil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2001**),
Ácido propano-1-sulfónico [3-(4-cloro-5-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2002**),
Ácido propano-1-sulfónico [3-(4-ciano-5-fluoro-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2003**),
Ácido propano-1-sulfónico [3-(5-ciano-4-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2005**),
Ácido propano-1-sulfónico [3-(5-cloro-4-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2007**),
Ácido propano-1-sulfónico [3-(5-cloro-4-metil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida (**P-2008**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0088] En una modalidad, el pan inhibidor de Raf es un compuesto seleccionado del grupo que consiste en:
N-{2,4-Difluoro-3-[4-(4-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1069**),
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1104**),
N-[3-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1107**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1111**),
N-[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1135**),

N-{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1136**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1137**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1138**),
N-{2,4-Difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida (**P-1139**),
N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1140**),
N-[2,4-Difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1141**),
N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1142**),
N-{3-[4-(1,3-Dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-1143**),
N-[3-(4-Ciclopropilmetoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1181**),
N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1182**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0089] En una modalidad, el pan inhibidor de Raf es un compuesto seleccionado del grupo que consiste en:
N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1070**),
N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1071**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1073**),
N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1103**),
N-[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1144**),
N-{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida (**P-1145**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1146**),
N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (**P-1147**),
N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-

bencenosulfonamida (**P-1148**),
N-{2,4-Difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida (**P-1149**),
N-{2,4-Difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida (**P-1150**),
N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1151**),
N-[2,4-Difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1152**),
N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1153**),
N-{3-[4-(1,3-Dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1154**), y

cualquier sal farmacéuticamente aceptable de los mismos.

[0090] En un décimo tercer aspecto, se proporcionan composiciones que incluyen una cantidad terapéuticamente efectiva de uno cualquiera o más compuestos como se describe en este documento, y por lo menos un portador, excipiente, y/o diluyente farmacéuticamente aceptable, incluyendo combinaciones de dos cualesquiera o más compuestos como se describe en este documento. La composición además puede incluir una pluralidad de diferentes compuestos farmacológicamente activos, los cuales pueden incluir una pluralidad de compuestos, como se describe en este documento. En ciertas modalidades, la composición puede incluir uno cualquiera o más compuestos, como se describe en este documento, en conjunto con uno o más compuestos que son terapéuticamente efectivos para la misma indicación de enfermedad. En una modalidad, la composición incluye uno cualquiera o más compuestos como se describe en este documento, en conjunto con uno o más compuestos que son terapéuticamente efectivos para la misma indicación de enfermedad, en donde los compuestos tienen un efecto sinérgico sobre la indicación de enfermedad. En una modalidad, la composición incluye uno cualquiera o más compuestos, como se describe en este documento, efectivos para tratar un cáncer y uno o más compuestos diferentes que son efectivos para tratar el mismo cáncer, en donde además los compuestos son sinérgicamente efectivos para tratar el cáncer.

[0091] En un décimo cuarto aspecto, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por una o más cinasas Raf (incluyendo cinasas A-Raf, B-Raf, y c-Raf-1), incluyendo mutaciones de las mismas, en un sujeto en necesidad de ello al administrar al sujeto una cantidad efectiva de una composición que incluye cualquiera o más compuestos como se describe en este documento. En una modalidad, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por una o más cinasas Raf, incluyendo mutaciones de las mismas, al administrar al sujeto una cantidad efectiva de una composición que incluye cualquiera o más compuestos como se describe en este documento en combinación con una o más terapias adecuadas diferentes para tratar la enfermedad.

[0092] En un decimo quinto aspecto, la invención proporciona métodos para tratar una enfermedad o condición mediado por cinasa A-Raf, incluyendo cualquier mutación de la misma, en un sujeto en necesidad de ello al administrar al sujeto una cantidad efectiva de una composición que incluye cualquiera o más compuestos como se describe en este documento. En una modalidad, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por una cinasa A-Raf, incluyendo cualquier mutación de la misma, al administrar al sujeto una cantidad efectiva de una composición que incluye cualquiera o más compuestos como se describe en este documento en combinación con una o más terapias adecuadas diferentes para tratar la enfermedad.

[0093] En un decimo sexto aspecto, la invención proporciona métodos para tratar una enfermedad o condición mediado por cinasa B-Raf, incluyendo cualquier mutación de la misma, en un sujeto en necesidad de ello al administrar al sujeto una cantidad efectiva de una composición que incluye cualquiera o más compuestos como se describe en este documento. En una modalidad, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por una cinasa B-Raf, incluyendo cualquier mutación de la misma, al administrar al sujeto una cantidad efectiva de una composición que incluye cualquiera o más compuestos como se describe en este documento en combinación con una o más terapias adecuadas diferentes para tratar la enfermedad.

[0094] En un decimo séptimo aspecto, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por la cinasa mutante B-Raf V600E, en un sujeto en necesidad de ello al administrar al sujeto una cantidad efectiva de una composición que incluye cualquiera o más compuestos como se describe en este documento. En una modalidad, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por una cinasa mutante B-Raf V600E, al administrar al sujeto una cantidad efectiva de una composición que incluye cualquiera o más compuestos como se describe en este documento en combinación con una o más terapias adecuadas diferentes para tratar la enfermedad. En una modalidad, la invención proporciona métodos para tratar un cáncer mediado por la mutante B-Raf V600E al administrar al sujeto una cantidad efectiva de una composición que incluye cualquiera o más compuestos como se describe en este documento. En una modalidad, la invención proporciona métodos para tratar un cáncer mediado por la mutante B-Raf V600E al administrar al sujeto una cantidad efectiva de una composición que incluye cualquiera o más compuestos como se describe en este documento en combinación con una o más terapias anti cáncer adecuadas, tal como uno o más fármacos quimioterapéuticos.

[0095] En un decimo octavo aspecto, la invención proporciona métodos para tratar una enfermedad o condición mediado por cinasa c-Raf-1, incluyendo cualquier mutación de la misma, en un sujeto en necesidad de ello al administrar al sujeto una cantidad efectiva de una composición que incluye cualquiera o más compuestos como se describe en este documento. En una modalidad, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por una cinasa c-Raf-1, incluyendo cualquier mutación de la misma, al administrar al sujeto una cantidad efectiva de una composición que incluye cualquiera o más compuestos como se describe en este documento en combinación con una o más terapias adecuadas diferentes para tratar la enfermedad.

[0096] En un decimo noveno aspecto, la invención proporciona un método para tratar un cáncer en un sujeto en necesidad de ello al administrar al sujeto una cantidad efectiva de una composición que incluye cualquiera o más compuestos como se describe en este documento.] En una modalidad, la invención proporciona un método para tratar un cáncer en un sujeto en necesidad de ello, al administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos, como se describe en este documento, en combinación con una o más terapias o procedimientos médicos diferentes, efectivos para tratar el cáncer. Otras terapias o procedimientos médicos incluyen terapia anti cáncer adecuada (por ejemplo, terapia farmacológica, terapia con vacunas, terapia génica, terapia fotodinámica) o procedimiento médico (por ejemplo, cirugía, tratamiento con radiación, calefacción hipertérmica, trasplante de médula ósea o células madre). En una modalidad, la o las terapias anti cáncer o procedimientos médicos adecuados se seleccionan del tratamiento con un agente quimioterapéutico (por ejemplo, fármaco quimioterapéutico), tratamiento con radiación (por ejemplo, rayos x , rayos γ, o haz de electrones, protones, neutrones, o partículas α), calefacción hipertérmica (por ejemplo, microondas, ultrasonido, por radiofrecuencia), Terapia con vacunas (por ejemplo, vacuna de carcinoma hepatocelular gen AFP, vacuna de vector adenoviral AFP, AG-858, vacuna alogénica de cáncer de mama con secreción de GM-CSF, vacunas peptídicas de células dendríticas), terapia génica (por ejemplo, vector Ad5CMV-p53, adenovector que codifica MDA7, adenovirus 5-factor de necrosis tumoral alfa), terapia fotodinámica (por ejemplo, ácido aminolevulínico, texaferina de lutecio), cirugía, o trasplante de médula ósea y células madre.

[0097] En un vigésimo aspecto, la invención proporciona una composición farmacéutica que incluye un compuesto y otro fármaco/agente, en donde el compuesto utilizado en la combinación incluye aquellos como se describe en este documento, por ejemplo, como se define en las reivindicaciones y describe en la Fórmula I, Fórmula II, Fórmula III, Fórmula IIIa, Tabla I, o Tabla II. La invención además proporciona un método para tratar una enfermedad o padecimiento mediado por proteína cinasa Raf en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto y otro fármaco o una sal farmacéuticamente aceptable del mismo, en donde el compuesto utilizado en la combinación incluye aquellos como se describe en este documento, por ejemplo, como se define en las reivindicaciones y describe en la Fórmula I, Fórmula II, Fórmula III, Fórmula IIIa, Tabla I, o Tabla II. En algunas modalidades, la invención proporciona una composición para, o un método para, tratar un cáncer en un sujeto en necesidad de ello al administrar al sujeto una cantidad efectiva de una composición que incluye cualquiera o más compuestos como se describe en este documento en combinación con uno o más agentes quimioterapéuticos adecuados. En una modalidad, el o los agentes quimioterapéuticos adecuados se seleccionan de un agente alquilante, incluyendo, pero sin limitarse a, adozelesina, altretamina, bendamustina, bizelesina, busulfano, carboplatina, carbocuona, carmofur, carmustina, clorambucil, cisplatina, ciclofosfamida, dacarbazina, estramustina, etoglucid, fotemustina, hepsulfamo, ifosfamida, improsulfano, irofulveno, lomustina, manosulfano, mecloretamina, melfalano, mitobronitol, nedaplatina, nimustina, oxaliplatina, piposulfano, prednimustina, procarbazina, ranimustina, satraplatina, semustina, estreptozocina, temozolomida, tiotepa, treosulfano, triazicuona, trietilenmelamina, tetranitrato de triplatina, trofosfamida, y uramustina; un antibiótico, incluyendo, pero sin limitarse a, aclarubicina, amrubicina, bleomicina, dactinomicina, daunorubicina, doxorubicina, elsamitrucina, epirubicina,

idarubicina, menogaril, mitomicina, neocarzinostatina, pentostatina, pirarubicina, plicamicina, valrubicina, y zorubicina; un antimetabolito, incluyendo, pero sin limitarse a, aminopterina, azacitidina, azatioprina, capecitabina, cladribina, clofarabina, citarabina, decitabina, floxuridina, fludarabina, 5-fluorouracilo, gemcitabina, hidroxiurea, mercaptopurina, metotrexato, nelarabina, pemetrexed, raltitrexed, tegafur-uracilo, tioguanina, trimetoprim, trimetrexato, y vidarabina; una inmunoterapia, incluyendo, pero sin limitarse a, alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, panitumumab, pertuzumab, rituximab, tositumomab, trastuzumab, 90 Y ibritumomab tiuxetano, ipilimumab, y tremelimumab; una hormona o antagonista de hormonas, incluyendo, pero sin limitarse a, anastrozol, andrógenos, buserelina, dietilestilbestrol, exemestano, flutamida, fulvestrant, goserelina, idoxifeno, letrozol, leuprólido, magestrol, raloxifeno, tamoxifeno, y toremifeno; un taxano, incluyendo, pero sin limitarse a, DJ-927, docetaxel, TPI 287, larotaxel, ortataxel, paclitaxel, DHA-paclitaxel, y tesetaxel; un retinoide, incluyendo, pero sin limitarse a, alitretinoina, bexaroteno, fenretinida, isotretinoina, y tretinoina; un alcaloide, incluyendo, pero sin limitarse a, demecolcina, homoharringtonina, vinblastina, vincristina, vindesina, vinflunina, y vinorelbina; un agente antiangiogénico, incluyendo, pero sin limitarse a, AE-941 (GW786034, Neovastat), ABT-510, 2-metoxiestradiol, lenalidomida, y talidomida; un inhibidor de topoisomerasa, incluyendo, pero sin limitarse a, amsacrina, belotecano, edotecarina, etopósido, fosfato de etopósido, exatecano, irinotecano (también metabolito activo SN-38 (7-etil-10-hidroxi-camptotecina)), lucantona, mitoxantrona, pixantrona, rubitecano, tenipósido, topotecano, y 9-aminocamptotecina; un inhibidor de cinasas, incluyendo, pero sin limitarse a, axitinib (AG 013736), dasatinib (BMS 354825), erlotinib, gefitinib, flavopiridol, mesilato de imatinib, lapatinib, difosfato de motesanib (AMG 706), nilotinib (AMN107), seliciclib, sorafenib, malato de sunitinib, AEE-788, BMS-599626, UCN-01 (7-hidroxistaurosporina), y vatalanib; un inhibidor orientado de la transducción de señales incluyendo, pero sin limitarse a bortezomib, geldanamicina, y rapamicina; un modificador de respuestas biológicas, incluyendo, pero sin limitarse a, imiquimod, interferón-α, e interleucina-2; y otros quimioterapéuticos, incluyendo, pero sin limitarse a 3-AP (3-amino-2-carboxialdehído tiosemicarbazona), altrasentan, aminoglutetimida, anagrelida, asparaginasa, briostatina-1, cilengitida, elesclomol, mesilato de eribulina (E7389), ixabepilona, lonidamina, masoprocol, mitoguanazona, oblimersen, sulindaco, testolactona, tiazofurina, inhibidores de mTOR (por ejemplo, temsirolimus, everolimus, deforolimus), inhibidores de PI3K (por ejemplo, BEZ235, GDC-0941, XL147, XL765), inhibidores de Cdk4 (por ejemplo, PD-332991), inhibidores de Akt, inhibidores de Hsp90 (por ejemplo, tanespimicina) e inhibidores de farnesiltransferasa (por ejemplo, tipifarnib). Preferentemente, el método para tratar un cáncer implica administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos como se describe en este documento, en combinación con un agente quimioterapéutico seleccionado de capecitabina, 5-fluorouracilo, carboplatina, dacarbazina, gefitinib, oxaliplatina, paclitaxel, SN-38, temozolomida, vinblastina, bevacizumab, cetuximab, interferón-α, interleucina--2, o erlotinib.

[0098] En un vigésimo primer aspecto, la invención proporciona un método para tratar una enfermedad o padecimiento en un sujeto en necesidad de ello, al administrar al sujeto una cantidad terapéuticamente efectiva de uno cualquiera o más compuestos como se describe en este documento, un profármaco de tal compuesto, una sal farmacéuticamente aceptable de tal compuesto o profármaco, o una formulación

farmacéuticamente aceptable de tal compuesto o profármaco. El compuesto puede estar solo o puede formar parte de una composición. En una modalidad, la invención proporciona un método para tratar una enfermedad o padecimiento en un sujeto, al administrar al sujeto una cantidad terapéuticamente efectiva de uno cualquiera o más compuestos, como se describe en este documento, un profármaco de tal compuesto, una sal farmacéuticamente aceptable de tal compuesto o profármaco, o una formulación farmacéuticamente aceptable de tal compuesto o profármaco en combinación con una o más terapias diferentes, adecuadas para la enfermedad o padecimiento.

[0099] En un vigésimo segundo aspecto, la invención proporciona kits que incluyen un compuesto o composición del mismo, como se describe en este documento. En algunas modalidades, el compuesto o composición se empaca, por ejemplo, en un vial, botella, frasco, el cual además puede empacarse, por ejemplo, dentro de una caja, envoltura, o bolsa; el compuesto o composición se aprueba por la Administración de Alimentos y Fármacos de E. U. o entidad reguladora similar para su administración a un mamífero, por ejemplo, un humano; el compuesto o composición se aprueba para su administración a un mamífero, por ejemplo, un humano, para una enfermedad o padecimiento mediado por proteína cinasas; el kit de la invención incluye instrucciones escritas para su uso y/u otra indicación de que el compuesto o composición es adecuada o se aprueba para su administración a un mamífero, por ejemplo, un humano, para una enfermedad o padecimiento mediado por proteína cinasas Raf; y el compuesto o composición se empaca en forma de dosis unitaria o dosis única, por ejemplo, píldoras, cápsulas, o similares de dosis única.

[0100] En aspectos y modalidades que implican el tratamiento de una enfermedad o padecimiento con cualquiera o más compuestos como se describe en este documento, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por A-Raf, mediado por B-Raf y/o mediado por c-Raf-1 en un sujeto en necesidad de ello (por ejemplo, un mamífero tal como un humano, otros primates, animales para deportes, animales de interés comercial tal como ganado, animales de granja tales como caballos, o mascotas tales como perros y gatos), por ejemplo, una enfermedad o padecimiento caracterizado por actividad anormal de A-Raf, B-Raf, y/o c-Raf-1 (por ejemplo, actividad de cinasa). En algunas modalidades, los métodos de la invención pueden implicar administrar al sujeto que adolece de o que está en riesgo de una enfermedad o padecimiento mediado por A-Raf, mediado por B-Raf y/o mediado por c-Raf-1, una cantidad efectiva de cualquiera o más inhibidores de Raf como se describe en este documento. En una modalidad, la enfermedad mediada por A-Raf, mediada por B-Raf, y/o mediada por c-Raf-1 se selecciona del grupo que consiste en enfermedades neurológicas, incluyendo, pero sin limitarse a, demencia vascular, lesión en cabeza, lesión en médula espinal, enfermedad de Alzheimer (AD), enfermedad de Parkinson, ataques y epilepsia; enfermedades neoplásicas incluyendo, pero sin limitarse a, melanoma, glioma, sarcoma, carcinoma (por ejemplo, gastrointestinal, de hígado, conducto biliar (colangiocarcinoma), colorectal, pulmón, mama, pancreático, tiroideo, renal, ovárico, próstata), linfoma (por ejemplo, linfoma histiocítico) neurofibromatosis, leucemia mieloide aguda, síndrome mielodisplásico, leucemia, angiogénesis tumoral, tumores neuroendocrinos tales como cáncer de tiroides medular, carcinoide, cáncer de pulmón de células pequeñas, sarcoma de Kaposi, y feocromocitoma; dolor de origen neuropático o inflamatorio, incluyendo, pero sin limitarse a, dolor agudo, dolor crónico, dolor relacionado con cáncer, y migraña; enfermedades cardiovasculares incluyendo, pero sin limitarse a, falla

cardiaca, apoplejía isquémica, hipertrofia cardiaca, trombosis (por ejemplo, síndromes de microangiopatía trombótica), ateroesclerosis, y lesión por reperfusión; inflamación y/o proliferación incluyendo, pero sin limitarse a, psoriasis, eczema, artritis y enfermedades y padecimientos autoinmunes, osteoartritis, endometriosis, cicatrización, restenosis vascular, trastornos fibróticos, artritis reumatoide, enfermedad intestinal inflamatoria (IBD); enfermedades por inmunodeficiencias, incluyendo, pero sin limitarse a, rechazo de transplantes de órganos, enfermedad injerto versus huésped, y sarcoma de Kaposi asociado con HIV; enfermedades renales, quísticas, o prostáticas, incluyendo, pero sin limitarse a, nefropatía diabética, enfermedad renal poliquística, nefroesclerosis, glomerulonefritis, hiperplasia de próstata, enfermedad de hígado poliquístico, esclerosis tuberosa, enfermedad de Von Hippel Lindau, enfermedad renal medular quística, nefronoftisis, y fibrosis quística; trastornos metabólicos, incluyendo, pero sin limitarse a, obesidad; infección, incluyendo, pero sin limitarse a, *Helicobacter pylori*, virus de Hepatitis e Influenza, fiebre, HIV, y septicemia; enfermedades pulmonares incluyendo, pero sin limitarse a, enfermedad pulmonar obstructiva crónica (COPD) y síndrome de insuficiencia respiratoria aguda (ARDS); enfermedades genéticas del desarrollo, incluyendo, pero sin limitarse a, síndrome de Noonan, síndrome de Costello, (síndrome faciocutaneoesquelético), síndrome LEOPARD, síndrome cardio-faciocutáneo (CFC), y anormalidades del síndrome de crestas neurales que provocan enfermedades cardiovasculares, esqueléticas, intestinales, de piel, cabello y endocrinas; y enfermedades asociadas con regeneración o degeneración muscular, incluyendo, pero sin limitarse a, sarcopenia, distrofias musculares (incluyendo, pero sin limitarse a, Distrofias de Duchenne, Becker, Emery-Dreifuss, de Cintura Pélvica, Facioescapulohumeral, Miotónica, Oculofaríngea, Distal y Muscular Congénita), enfermedades de neuronas motoras (incluyendo, pero sin limitarse a, esclerosis lateral amiotrófica, atrofia muscular espinal progresiva infantil, atrofia muscular espinal intermedia, atrofia muscular espinal juvenil, atrofia muscular bulbar espinal, y atrofia muscular espinal adulta), miopatías inflamatorias (incluyendo, pero sin limitarse a, dermatomiositis, polimiositis, y miositis por cuerpos de inclusión), enfermedades de la placa neuromuscular (incluyendo, pero sin limitarse a, miastenia grave, síndrome de Lambert-Eaton, y síndrome miasténico congénito), miopatías debido a anormalidades endocrinas (incluyendo, pero sin limitarse a, miopatía hipertiroidea y miopatía hipotiroidea) enfermedades de nervios periféricos (incluyendo, pero sin limitarse a, enfermedad de Charcot Marie Tooth, enfermedad de Dejerine-Sottas, y ataxia de Friedreich), otras miopatías (incluyendo, pero sin limitarse a, miotonía congénita, paramiotonía congénita, enfermedad de núcleo central, miopatía nemalínica, miopatía miotubular, y parálisis periódica), y enfermedades metabólicas de músculo (incluyendo, pero sin limitarse a, deficiencia de fosforilasa, deficiencia de maltasa ácida, deficiencia de fosfofructocinasa, deficiencia de enzima de desconexión, miopatía mitocondrial, deficiencia de carnitina, deficiencia de carnitina palmatilo transferasa, deficiencia de fosfoglicerato cinasa, deficiencia de fosfoglicerato mutasa, deficiencia de lactato deshidrogenasa, y deficiencia de mioadenilato desaminasa). En una modalidad, la enfermedad o padecimiento se selecciona del grupo que consiste en melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, sarcoma, cáncer de hígado, cáncer del tracto biliar, colangiocarcinoma, cáncer colorrectal, cáncer de pulmón, cáncer de vesícula biliar, cáncer de mama, cáncer pancreático, cáncer de tiroides, cáncer renal, cáncer ovárico, cáncer adrenocortical, cáncer de próstata, linfoma histiocítico, neurofibromatosis, tumores de estroma gastrointestinal, leucemia mieloide aguda, síndrome mielodisplásico, leucemia, angiogénesis tumoral, cáncer de tiroides medular, carcinoide, cáncer pulmonar

de células pequeñas, sarcoma de Kaposi, feocromocitoma, dolor agudo, dolor crónico, y enfermedad renal poliquística. En una modalidad preferida, la enfermedad o padecimiento se selecciona del grupo que consiste en melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, cáncer colorrectal, cáncer de tiroides, cáncer de pulmón, cáncer ovárico, cáncer de próstata, cáncer de hígado, cáncer de vesícula biliar, tumores de estroma gastrointestinal, cáncer del tracto biliar, colangiocarcinoma, dolor agudo, dolor crónico, y enfermedad renal poliquística.

[0101] En aspectos y modalidades que implican el tratamiento de una enfermedad o padecimiento con cualquiera o más compuestos como se describe en este documento, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por c-Raf-1 en un sujeto en necesidad de ello (por ejemplo, un mamífero tal como un humano, otros primates, animales para deportes, animales de interés comercial tal como ganado, animales de granja tales como caballos, o mascotas tales como perros y gatos), por ejemplo, una enfermedad o padecimiento caracterizado por actividad anormal de c-Raf-1 (por ejemplo, actividad de cinasa). En algunas modalidades, los métodos de la invención pueden implicar administrar al sujeto que adolece de o que está en riesgo de una enfermedad o padecimiento mediado por c-Raf-1, una cantidad efectiva de cualquiera o más inhibidores de c-Raf-1 como se describe en este documento. En una modalidad, la enfermedad mediada por c-Raf-1 se selecciona del grupo que consiste en enfermedad renal poliquística, dolor agudo, y dolor crónico.

[0102] En aspectos y modalidades que implican el tratamiento de una enfermedad o padecimiento con cualquiera o más compuestos como se describe en este documento, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por la mutante B-Raf V600E en un sujeto en necesidad de ello (por ejemplo, un mamífero tal como un humano, otros primates, animales para deportes, animales de interés comercial tal como ganado, animales de granja tales como caballos, o mascotas tales como perros y gatos), por ejemplo, una enfermedad o padecimiento caracterizado por actividad de la mutante B-Raf V600E (por ejemplo, actividad de cinasa). En algunas modalidades, los métodos de la invención pueden implicar administrar al sujeto que adolece de o que está en riesgo de una enfermedad o padecimiento mediado por la mutante B-Raf V600E, una cantidad efectiva de cualquiera o más inhibidores de B-Raf V600E como se describe en este documento. En una modalidad, la enfermedad mediada por la mutante B-Raf V600E es un cáncer, preferiblemente un cáncer seleccionado del grupo que consiste en melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, cáncer colorrectal, cáncer de tiroides, cáncer de pulmón, cáncer ovárico, cáncer de próstata, cáncer de hígado, cáncer de vesícula biliar, tumores de estroma gastrointestinal, cáncer del tracto biliar, y colangiocarcinoma.

[0103] En aspectos y modalidades que implican el tratamiento de una enfermedad o padecimiento con cualquiera o más compuestos como se describe en este documento, la invención proporciona métodos para tratar un cáncer en un sujeto en necesidad de ello (por ejemplo, un mamífero tal como un humano, otros primates, animales para deportes, animales de interés comercial tal como ganado, animales de granja tales como caballos, o mascotas tales como perros y gatos). En algunas modalidades, los métodos de la invención pueden implicar administrar al sujeto que adolece de o que está en riesgo de un cáncer, una cantidad efectiva de uno cualquiera o más pan inhibidores de Raf, como se describe en este documento, en donde el cáncer se selecciona del grupo que consiste en melanoma, glioma, glioblastoma,

astrocitoma pilocítico, cáncer de hígado, cáncer del tracto biliar, colangiocarcinoma, cáncer colorrectal, cáncer de pulmón, cáncer de vejiga, cáncer de vesícula biliar, cáncer de mama, cáncer pancreático, cáncer de tiroides, cáncer de riñón, cáncer ovárico, cáncer adrenocortical, cáncer de próstata, tumores de estroma gastrointestinal, cáncer de tiroides medular, angiogénesis tumoral, leucemia mieloide aguda, leucemia mielomonocítica crónica, leucemia linfoblástica aguda de la niñez, leucemia de células plasmáticas, y mieloma múltiple.

[0104] En un vigésimo tercer aspecto, cualquiera o más compuestos como se describe en este documento pueden utilizarse en la preparación de un medicamento para el tratamiento de una enfermedad o padecimiento mediado por A-Raf, mediado por B-Raf o mediado por c-Raf-1 seleccionado del grupo que consiste en enfermedades neurológicas, incluyendo, pero sin limitarse a, demencia vascular, lesión en cabeza, lesión en médula espinal, enfermedad de Alzheimer (AD), enfermedad de Parkinson, ataques y epilepsia; enfermedades neoplásicas incluyendo, pero sin limitarse a, melanoma, glioma, sarcoma, carcinoma (por ejemplo, gastrointestinal, de hígado, conducto biliar (colangiocarcinoma), colorectal, pulmón, mama, pancreático, tiroideo, renal, ovárico, próstata), linfoma (por ejemplo, linfoma histiocítico) neurofibromatosis, leucemia mieloide aguda, síndrome mielodisplásico, leucemia, angiogénesis tumoral, tumores neuroendocrinos tales como cáncer de tiroides medular, carcinoide, cáncer de pulmón de células pequeñas, sarcoma de Kaposi, y feocromocitoma; dolor de origen neuropático o inflamatorio, incluyendo, pero sin limitarse a, dolor agudo, dolor crónico, dolor relacionado con cáncer, y migraña; enfermedades cardiovasculares incluyendo, pero sin limitarse a, falla cardiaca, apoplejía isquémica, hipertrofia cardiaca, trombosis (por ejemplo, síndromes de microangiopatía trombótica), ateroesclerosis, y lesión por reperfusión; inflamación y/o proliferación incluyendo, pero sin limitarse a, psoriasis, eczema, artritis y enfermedades y padecimientos autoinmunes, osteoartritis, endometriosis, cicatrización, restenosis vascular, trastornos fibróticos, artritis reumatoide, enfermedad intestinal inflamatoria (IBD); enfermedades por inmunodeficiencias, incluyendo, pero sin limitarse a, rechazo de transplantes de órganos, enfermedad injerto versus huésped, y sarcoma de Kaposi asociado con HIV; enfermedades renales, quísticas, o prostáticas, incluyendo, pero sin limitarse a, nefropatía diabética, enfermedad renal poliquística, nefroesclerosis, glomerulonefritis, hiperplasia de próstata, enfermedad de hígado poliquístico, esclerosis tuberosa, enfermedad de Von Hippel Lindau, enfermedad renal medular quística, nefronoftisis, y fibrosis quística; trastornos metabólicos, incluyendo, pero sin limitarse a, obesidad; infección, incluyendo, pero sin limitarse a, *Helicobacter pylori*, virus de Hepatitis e Influenza, fiebre, HIV, y septicemia; enfermedades pulmonares incluyendo, pero sin limitarse a, enfermedad pulmonar obstructiva crónica (COPD) y síndrome de insuficiencia respiratoria aguda (ARDS); enfermedades genéticas del desarrollo, incluyendo, pero sin limitarse a, síndrome de Noonan, síndrome de Costello, (síndrome faciocutaneoesquelético), síndrome LEOPARD, síndrome cardio-faciocutáneo (CFC), y anormalidades del síndrome de crestas neurales que provocan enfermedades cardiovasculares, esqueléticas, intestinales, de piel, cabello y endocrinas; y enfermedades asociadas con regeneración o degeneración muscular, incluyendo, pero sin limitarse a, sarcopenia, distrofias musculares (incluyendo, pero sin limitarse a, Distrofias de Duchenne, Becker, Emery-Dreifuss, de Cintura Pélvica, Facioescapulohumeral, Miotónica, Oculofaríngea, Distal y Muscular Congénita), enfermedades de neuronas motoras (incluyendo, pero sin limitarse a, esclerosis lateral amiotrófica, atrofia muscular espinal

progresiva infantil, atrofia muscular espinal intermedia, atrofia muscular espinal juvenil, atrofia muscular bulbar espinal, y atrofia muscular espinal adulta), miopatías inflamatorias (incluyendo, pero sin limitarse a, dermatomiositis, polimiositis, y miositis por cuerpos de inclusión), enfermedades de la placa neuromuscular (incluyendo, pero sin limitarse a, miastenia grave, síndrome de Lambert-Eaton, y síndrome miasténico congénito), miopatías debido a anormalidades endocrinas (incluyendo, pero sin limitarse a, miopatía hipertiroidea y miopatía hipotiroidea) enfermedades de nervios periféricos (incluyendo, pero sin limitarse a, enfermedad de Charcot Marie Tooth, enfermedad de Dejerine-Sottas, y ataxia de Friedreich), otras miopatías (incluyendo, pero sin limitarse a, miotonía congénita, paramiotonía congénita, enfermedad de núcleo central, miopatía nemalínica, miopatía miotubular, y parálisis periódica), y enfermedades metabólicas de músculo (incluyendo, pero sin limitarse a, deficiencia de fosforilasa, deficiencia de maltasa ácida, deficiencia de fosfofructocinasa, deficiencia de enzima de desconexión, miopatía mitocondrial, deficiencia de carnitina, deficiencia de carnitina palmatilo transferasa, deficiencia de fosfoglicerato cinasa, deficiencia de fosfoglicerato mutasa, deficiencia de lactato deshidrogenasa, y deficiencia de mioadenilato desaminasa). En una modalidad, la enfermedad o padecimiento se selecciona del grupo que consiste en melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, sarcoma, cáncer de hígado, cáncer del tracto biliar, colangiocarcinoma, cáncer colorrectal, cáncer de pulmón, cáncer de vesícula biliar, cáncer de mama, cáncer pancreático, cáncer de tiroides, cáncer renal, cáncer ovárico, cáncer adrenocortical, cáncer de próstata, linfoma histiocítico, neurofibromatosis, tumores de estroma gastrointestinal, leucemia mieloide aguda, síndrome mielodisplásico, leucemia, angiogénesis tumoral, cáncer de tiroides medular, carcinoide, cáncer pulmonar de células pequeñas, sarcoma de Kaposi, feocromocitoma, dolor y enfermedad renal poliquística. En una modalidad preferida, la enfermedad o padecimiento se selecciona del grupo que consiste en melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, cáncer colorrectal, cáncer de tiroides, cáncer de pulmón, cáncer ovárico, cáncer de próstata, cáncer de hígado, cáncer de vesícula biliar, tumores de estroma gastrointestinal, cáncer del tracto biliar, colangiocarcinoma, dolor agudo, dolor crónico, y enfermedad renal poliquística.

[0105] En un vigésimo cuarto aspecto, cualquiera o más inhibidores de c-Raf-1 como se describe en este documento puede utilizarse en la preparación de un medicamento para el tratamiento de una enfermedad o padecimiento mediado por c-Raf-1 seleccionado del grupo que consiste en dolor agudo, dolor crónico, y enfermedad renal poliquística.

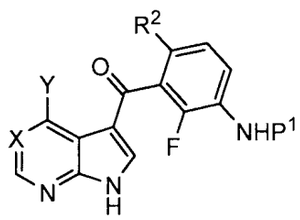
[0106] En un vigésimo quinto aspecto, cualquiera o más inhibidores de B-Raf V600E como se describe en este documento puede utilizarse en la preparación de un medicamento para el tratamiento de una enfermedad o padecimiento mediado por B-Raf-V600E seleccionado del grupo que consiste en melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, cáncer colorrectal, cáncer de tiroides, cáncer de pulmón, cáncer ovárico, cáncer de próstata, cáncer de hígado, cáncer de vesícula biliar, tumores de estroma gastrointestinal, cáncer del tracto biliar, y colangiocarcinoma.

[0107] En un vigésimo sexto aspecto, cualquiera o más pan inhibidores de Raf como se describe en este documento puede utilizarse en la preparación de un medicamento para el tratamiento de un cáncer seleccionado del grupo que consiste en melanoma, glioma, glioblastoma, astrocitoma pilocítico, cáncer de

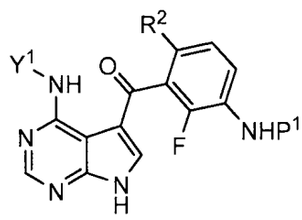
hígado, cáncer del tracto biliar, colangiocarcinoma, cáncer colorrectal, cáncer de pulmón, cáncer de vejiga, cáncer de vesícula biliar, cáncer de mama, cáncer pancreático, cáncer de tiroides, cáncer de riñón, cáncer ovárico, cáncer adrenocortical, cáncer de próstata, tumores de estroma gastrointestinal, cáncer de tiroides medular, angiogénesis tumoral, leucemia mieloide aguda, leucemia mielomonocítica crónica, leucemia linfoblástica aguda de la niñez, leucemia de células plasmáticas, y mieloma múltiple.

[0108] En diversos aspectos y modalidades, un compuesto como se da a conocer en este documento (incluyendo cualquier compuesto de la Fórmula I, Fórmula II, Fórmula III, Fórmula IIIa, Tabla I, Tabla II, o cualquier otro compuesto específicamente dado a conocer en este documento) es un pan inhibidor de Raf.] En diversos aspectos y modalidades, un compuesto como se da a conocer en este documento (incluyendo cualquier compuesto de la Fórmula I, Fórmula II, Fórmula III, Fórmula IIIa, Tabla I, Tabla II, o cualquier otro compuesto específicamente dado a conocer en este documento) es un inhibidor de la actividad de Ras.] En algunas modalidades, un compuesto como se da a conocer en este documento (incluyendo cualquier compuesto de la Fórmula I, Fórmula II, Fórmula III, Fórmula IIIa, Tabla I, Tabla II, o cualquier otro compuesto específicamente dado a conocer en este documento) es tanto un pan inhibidor de Raf como un inhibidor de la actividad de Ras. En ciertas modalidades, un compuesto como se da a conocer en este documento (incluyendo cualquier compuesto de la Fórmula I, Fórmula II, Fórmula III, Fórmula IIIa, Tabla I, Tabla II o cualquier otro compuesto específicamente dado a conocer en este documento) es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E y es un inhibidor de la actividad de Ras que inhibe la proliferación de una línea celular mutante en Ras con una IC_{50} de menos de 1 μM.

[0109] En otro aspecto, la invención proporciona una intermediate compuesto de las Fórmulas IVa y IVb:



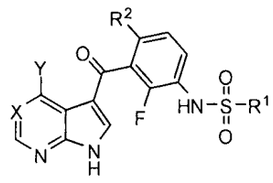
IVa



IVb

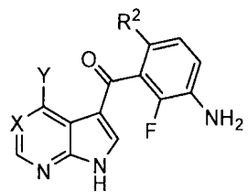
en donde P^1 es independientemente H o un grupo protector amino. En una modalidad, P^1 es H. En otra modalidad, P^1 es t-butoxicarbonilo o benciloxicarbonilo. En otra modalidad, X es –N=, –CH=, -C(CH_3)=, -C(OCH_3)=, -C(F)=, -C(CN)=, -C(CH_2OH)= o –C(Cl)=. En ciertos casos, X es –CH=. En otros casos, X es –N=. Los otros sustituyentes X, Y, Y^1 y R^2 son como se define en cualquiera de las modalidades para los compuestos de las Fórmulas I, II, III y IIIa descritos en este documento.

[0110] En otro aspecto, la invención proporciona un método para preparar un compuesto de la Fórmula I



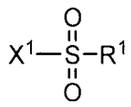
I

El método incluye poner en contacto un compuesto de la Fórmula IVc:



IVc

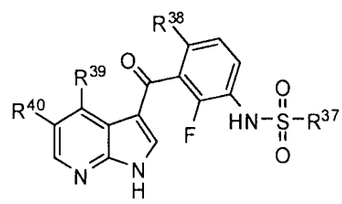
con un compuesto de la Fórmula V:



V

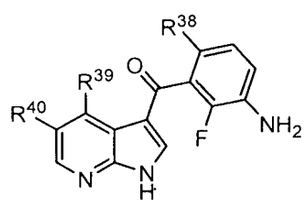
bajo condiciones suficientes para formar el compuesto de la Fórmula I, en donde X^1 es un halógeno, tal como Cl, Br o I, las otras variables R^1, R^2, X y Y son como se define en cualquiera de las modalidades para los compuestos de las Fórmulas I, II, III y IIIa descritos en este documento y en los Ejemplos a continuación. En algunas modalidades, X es –N=, –CH=, -C(CH_3)=, -C(OCH_3)=, -C(F)=, -C(CN)=, -C(CH_2OH)= o –C(Cl)=. En una modalidad preferida, R^1 es 2-fluorofenilo, 3-fluorofenilo, 2,5-difluorofenilo o fenilo 4-alquilo inferior-sustituido, en donde el alquilo inferior se sustituye opcionalmente con uno o más flúor.

[0111] En algunas modalidades, la invención proporciona un método para preparar un compuesto de la Fórmula II:



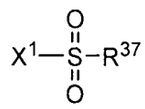
II

El método incluye poner en contacto un compuesto de la Fórmula IVd:



IVd

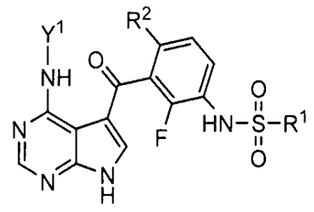
con un compuesto de la Fórmula Va:



Va

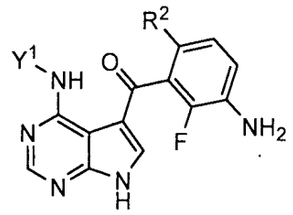
bajo condiciones adecuadas para formar el compuesto de la Fórmula I, en donde X^1 es un halógeno, tal como Cl, Br o I, las otras variables R^{37}, R^{38}, R^{39} y R^{40} son como se define en cualquiera de las modalidades para los compuestos de la Fórmula II descritos en este documento y en los Ejemplos a continuación. En una modalidad preferida, R^{37} es 2-fluorofenilo, 3-fluorofenilo, 2,5-difluorofenilo o fenilo 4-alquilo inferior-sustituido, en donde el alquilo inferior se sustituye opcionalmente con uno o más flúor.

[0112] En algunas modalidades, la invención proporciona un método para preparar un compuesto de la Fórmula IIIa:



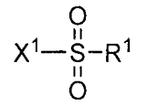
IIIa

El método incluye poner en contacto un compuesto de la Fórmula IVe:



IVe

con un compuesto de la Fórmula V:



V

bajo condiciones suficientes para formar el compuesto de la Fórmula I, en donde X^1 es un halógeno, tal como Cl, Br o I, las otras variables Y^1, R^1, y R^2 son como se define en cualquiera de las modalidades anteriores para los compuestos de las Fórmulas I y IIIa y en los Ejemplos a continuación. En una modalidad preferida, R^1 es 2-fluorofenilo, 3-fluorofenilo, 2,5-difluorofenilo o fenilo 4-alquilo inferior-sustituido, en donde el alquilo inferior se sustituye opcionalmente con uno o más flúor.

[0113] Aspectos y modalidades adicionales serán aparentes a partir de la siguiente Descripción Detallada de la Invención y de las reivindicaciones.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

[0114] Como se utilizan en este documento, las definiciones siguientes se aplican a menos que se indique claramente de otro modo:

[0115] Todos los átomos designados dentro de una Fórmula descrita en este documento, ya sea dentro de una estructura proporcionada, o dentro de las definiciones de las variables relacionadas con la estructura, tienen la intención de incluir cualquier isótopo de los mismos, a menos que se indique claramente lo contrario. Se entiende que, para cualquier átomo dado, los isótopos pueden presentarse esencialmente en las proporciones de acuerdo su ocurrencia natural, o uno o más átomos particulares pueden aumentarse con respecto a uno o más isótopos al utilizar los métodos sintéticos conocidos por un experto en la técnica. De esta manera, el hidrógeno incluye, por ejemplo, ^{1}H, ^{2}H, ^{3}H; el carbono incluye, por ejemplo, ^{11}C, ^{12}C, ^{13}C, ^{14}C; el oxígeno incluye, por ejemplo, ^{16}O, ^{17}O, ^{18}O; el nitrógeno incluye, por ejemplo, ^{13}N, ^{14}N, ^{15}N; el azufre incluye, por ejemplo, ^{32}S, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{37}S, ^{38}S; el flúor incluye, por ejemplo, ^{17}F, ^{18}F, ^{19}F; el cloro incluye, por ejemplo, ^{35}Cl, ^{36}Cl, ^{37}Cl, ^{38}Cl, ^{39}Cl; y similares.

[0116] "Halógeno" se refiere a todos los halógenos, es decir, cloro (Cl), flúor (F), bromo (Br), o yodo (I).

[0117] "Haloalquilo o Alquilo inferior sustituido con halógeno" incluye alquilo sustituido por uno a siete átomos de halógeno. Haloalquilo incluye monohaloalquilo y polihaloalquilo. Por ejemplo, el término "haloalquilo" quiere decir que incluye trifluorometilo, CF_3CH_2-, CF_2HCH_2-, 2,2,2-trifluoroetilo, 4-clorobutilo, 3-bromopropilo, y similares.

[0118] "Haloalcoxi" se refiere a un radical -OR donde R es el grupo haloalquilo como se define anteriormente, por ejemplo, trifluorometoxi, 2,2, 2-trifluoroetoxi, difluorometoxi, y similares.

[0119] "Hidroxilo" o "hidroxi" se refieren al grupo -OH.

[0120] "Tiol" se refiere al grupo -SH.

[0121] "Alquilo inferior", solo o en combinación, significa a un radical derivado de alcano que contiene de 1 a 6 átomos de carbono (a menos que se defina específicamente) que incluye un alquilo de cadena lineal o alquilo ramificado. El grupo alquilo inferior de cadena lineal o ramificado es químicamente accesible y se une en cualquier punto disponible para proporcionar un compuesto estable. En muchas modalidades, un alquilo inferior es un grupo alquilo lineal o ramificado que contiene de 1-6, 1-4, o 1-2, átomos de carbono, tales como metilo, etilo, propilo, isopropilo, butilo, t-butilo, y similares. Un alquilo inferior puede sustituirse independientemente, como se describe en este documento, a menos que se indique de otra manera, con uno o más, preferentemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustituyentes, en donde los sustituyentes son como se indica. Por ejemplo "alquilo inferior sustituido con flúor" denota un grupo alquilo inferior sustituido con uno o más átomos de flúor, tal como perfluoroalquilo, donde preferiblemente el alquilo inferior se sustituye con 1, 2, 3, 4 o 5 átomos de flúor, también 1, 2, o 3 átomos de flúor. Se entiende que cualquier sustitución semejante, o sustitución de alquilo inferior en otra porción, son químicamente factibles y se unen en cualquier átomo disponible para proporcionar un compuesto estable.

[0122] "Alquileno" por sí mismo o como parte de otro sustituyente significa un radical hidrocarburo divalente saturado lineal o ramificado derivado de un alcano que tiene el número de átomos de carbono indicados en el prefijo. Por ejemplo, (C_1-C_6)alquileno quiere decir que

incluye metileno, etileno, propileno, 2-metilpropileno, pentileno, hexileno, y similares. Típicamente, un grupo alquilo (o alquileno) tendrá de 1 a 24 átomos de carbono, y aquellos grupos que tienen 10, 8, 6, 4 o menos átomos de carbono se prefieren en la presente invención. Cuando un prefijo no se incluye para indicar el número de átomos de carbono en una porción alquilo o alquileno, el radical o porción del mismo tendrá 8 o menos átomos de carbono de la cadena principal o 6 o menos átomos de carbono de cadena principal o 4 o menos átomos de carbono de cadena principal.

[0123] "Alquenilo inferior", solo o en combinación, significa un hidrocarburo lineal o ramificado que contiene 2-6 átomos de carbono (a menos que se defina específicamente) y al menos uno, preferiblemente 1-3, más preferiblemente 1-2, muy preferiblemente uno, doble enlace carbono a carbono. Los dobles enlaces carbono a carbono pueden contenerse dentro de una cadena lineal o porción ramificada. El grupo alquenilo inferior de cadena lineal o ramificado es químicamente factible y se une en cualquier punto disponible para proporcionar un compuesto estable. Ejemplos de grupos alquenilo inferior incluyen etenilo, propenilo, isopropenilo, butenilo, y similares. Un "alquenilo inferior sustituido" denota alquenilo inferior que se sustituye independientemente, a menos que se indique de otra manera, con uno o más, preferiblemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustituyentes, en donde los sustituyentes son como se indica. Por ejemplo, "alquenilo inferior opcionalmente sustituido con $C(O)$-O-R^{28}" denota un grupo alquenilo inferior que puede sustituirse con una porción ácido carboxílico, es decir, $C(O)$-O-R^{28} se sustituye en el grupo alquenilo, donde el carbono de $C(O)$-O-R^{28} se une a un carbono del grupo alquenilo. Se entiende que cualquier sustitución semejante, o sustitución de alquenilo inferior en otra porción, son químicamente factibles y se unen en cualquier átomo disponible para proporcionar un compuesto estable.

[0124] "Alquinilo inferior", solo o en combinación, significa un hidrocarburo lineal o ramificado que contiene 2-6 átomos de carbono (a menos que se defina específicamente) que contiene al menos uno, preferiblemente uno, triple enlace carbono a carbono. El grupo alquinilo inferior de cadena lineal o ramificado es químicamente factible y se une en cualquier punto disponible para proporcionar un compuesto estable. Ejemplos de grupos alquinilo incluyen etinilo, propinilo, butinilo, y similares. Un "alquinilo inferior sustituido" denota alquinilo inferior que se sustituye independientemente, a menos que se indique de otra manera, con uno o más, preferiblemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustituyentes, en donde los sustituyentes son como se indica. Por ejemplo, "alquinilo inferior opcionalmente sustituido con R^9" denota un grupo alquinilo inferior que puede sustituirse con un sustituyente R^9. Se entiende que cualquier sustitución semejante, o sustitución de alquinilo inferior en otra porción, son químicamente factibles y se unen en cualquier átomo disponible para proporcionar un compuesto estable.

[0125] "Cicloalquilo" se refiere a sistemas de anillos de carbono saturados o insaturados, no aromáticos monocíclicos de 3-10, también 3-8, más preferiblemente 3-6, miembros de anillo por anillo, tales como ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, y similares. Un "cicloalquilo sustituido" es un cicloalquilo que se sustituye independientemente, a menos que se indique de otra manera, con uno o más, preferiblemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustituyentes, en donde los sustituyentes son como se

indica. Se entiende que las sustituciones en cicloalquilo, o sustitución de cicloalquilo en otra porción, son químicamente factibles y se unen en cualquier átomo disponible para proporcionar un compuesto estable.

[0126] "Cicloalquilalquilo" se refiere a un radical -(alquileno)-R, donde R es cicloalquilo como se define anteriormente, por ejemplo, ciclopropilmetilo, ciclobutiletilo, ciclobutilmetilo, y similares.

[0127] "Heterocicloalquilo" se refiere a un grupo cicloalquilo saturado o insaturado no aromático que tiene de 5 a 10 átomos en los que de 1 a 3 átomos de carbono en el anillo se reemplazan por heteroátomos de O, S o N, y se fusionan opcionalmente con benzo o heteroarilo de 5-6 miembros de anillo. Heterocicloalquilo también pretende incluir S o N oxidados, tales como sulfinilo, sulfonilo y N-óxido de un nitrógeno de anillo terciario. Heterocicloalquilo también pretende incluir compuestos en los cuales un carbono del anillo puede sustituirse con oxo, es decir, el carbono del anillo es un grupo carbonilo, tales como lactonas y lactamas. El punto de unión del anillo heterocicloalquilo está en un átomo de carbono o nitrógeno de tal modo que un anillo estable se retiene. Ejemplos de grupos heterocicloalquilo incluyen, pero no se limitan a, morfolino, tetrahidrofuranilo, dihidropiridinilo, piperidinilo, pirrolidinilo, pirrolidonilo, piperazinilo, dihidrobenzofurilo, dihidroindolilo, imidazolidinilo, pirazolidinilo, radical butirolactama, radical valerolactama, radical imidazolidinona, hidantoína, radical dioxolano, radical ftalimida, radical 1,4-dioxane, tiomorfolinilo, tiomorfolinil-S-óxido, tiomorfolinil-S,S-óxido, piperazinilo, piranilo, 3-pirrolinilo, tiopiranilo, radical pirona, tetrahidrotiofenilo, quinuclidinilo, y similares. Un "heterocicloalquilo sustituido" es un heterocicloalquilo que se sustituye independientemente, a menos que se indique de otra manera, con uno o más, preferiblemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustituyentes, en donde los sustituyentes son como se indica. Se entiende que las sustituciones en heterocicloalquilo, o sustitución de heterocicloalquilo en otra porción, son químicamente factibles y se unen en cualquier átomo disponible para proporcionar un compuesto estable. "Heterocicloalquilalquilo" se refiere a un radical -(alquileno)-R, donde R es heterocicloalquilo como se define en este documento.

[0128] "Arilo", solo o en combinación, se refiere a un sistema de anillos monocíclicos o bicíclicos que contiene hidrocarburos aromáticos tales como fenilo o naftilo, que puede fusionarse opcionalmente con un cicloalquilo de preferiblemente 5-7, más preferiblemente 5-6, miembros de anillo. Un "arilo sustituido" es un arilo que se sustituye independientemente, a menos que se indique de otra manera, con uno o más, preferiblemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustituyentes, en donde los sustituyentes son como se indica. Se entiende que las sustituciones en arilo, o sustitución de arilo en otra porción, son químicamente factibles y se unen en cualquier átomo disponible para proporcionar un compuesto estable.

[0129] "Aralquilo"se refiere a un radical -(alquileno)-R, donde R es arilo como se define anteriormente por ejemplo, bencilo, fenetilo, y similares.

[0130] "Heteroarilo", solo o en combinación, se refiere a una estructura de anillos aromáticos monocíclicos que contienen 5 o 6 átomos de anillo, o un grupo aromático bicíclico que tiene de 8 a 10 átomos, que contienen uno o más, preferiblemente 1-4, más preferiblemente 1-3, aún más preferiblemente 1-2, heteroátomos seleccionados independientemente del grupo que consiste en O, S, y N. Heteroarilo también pretende incluir S o N oxidados, tales como 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 heteroarilo de tal modo que se proporciona un compuesto estable. Ejemplos de grupos heteroarilo incluyen, pero no se limitan a, piridinilo, piridazinilo, pirazinilo, quinaoxalilo, indolizinilo, benzo[b]tienilo, quinazolinilo, purinilo, indolilo, quinolinilo, pirimidinilo, pirrolilo, pirazolilo, oxazolilo, tiazolilo, tienilo, isoxazolilo, oxatiadiazolilo, isotiazolilo, tetrazolilo, imidazolilo, triazolilo, furanilo, benzofurilo, e indolilo. Un "heteroarilo sustituido" es un heteroarilo que se sustituye independientemente, a menos que se indique de otra manera, con uno o más, preferiblemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustituyentes, en donde los sustituyentes son como se indica. Se entiende que las sustituciones en heteroarilo, o sustitución de heteroarilo en otra porción, son químicamente factibles y se unen en cualquier átomo disponible para proporcionar un compuesto estable.

[0131] "Heteroarilalquilo" se refiere a un radical –(alquileno)-R, donde R es un grupo heteroarilo como se define en este documento. Ejemplos f heteroarilalquilo incluyen 2-piridilmetilo, 2-tiazoliletilo, 4H, 1,2,4-triazolietilo, y similares.

[0132] "Alcoxi inferior" denota el grupo -OR^a, donde R^a es alquilo inferior. "Alcoxi inferior sustituido" denota alcoxi inferior en el que R^a es alquilo inferior sustituido con uno o más sustituyentes como se indica en este documento. Preferiblemente, la sustitución de alcoxi inferior es con 1, 2, 3, 4, o 5 sustituyentes, también 1, 2, o 3 sustituyentes. Por ejemplo, "alcoxi inferior sustituido con flúor" denota alcoxi inferior en el que el alquilo inferior se sustituye con uno o más átomos de flúor, donde preferiblemente el alcoxi inferior se sustituye con 1, 2, 3, 4 o 5 átomos de flúor, también 1, 2, o 3 átomos de flúor. Se entiende que las sustituciones en alcoxi, o sustitución de alcoxi en otra porción, son químicamente factibles y se unen en cualquier átomo disponible para proporcionar un compuesto estable.

[0133] "Alquiltio inferior" denota el grupo -SR^b, donde R^b es alquilo inferior. "Alquiltio inferior sustituido" denota alquiltio inferior en el que R^b es alquilo inferior sustituido con uno o más sustituyentes como se indica en este documento. Preferiblemente, la sustitución de alquiltio inferior es con 1, 2, 3, 4, o 5 sustituyentes, también 1, 2, o 3 sustituyentes. Por ejemplo, "alquiltio inferior sustituido con flúor" denota alquiltio inferior en el que el alquilo inferior se sustituye con uno o más átomos de flúor, donde preferiblemente el alquiltio inferior se sustituye con 1, 2, 3, 4 o 5 átomos de flúor, también 1, 2, o 3 átomos de flúor. Se entiende que las sustituciones en alquiltio, o sustitución de alquiltio en otra porción, son químicamente factibles y se unen en cualquier átomo disponible para proporcionar un compuesto estable.

[0134] Como se utiliza en este documento, "uno o más sustituyentes" específicamente contempla, entre otros, de uno a siete, más preferiblemente de uno a cinco, incluso más preferiblemente de uno a tres sustituyentes en un grupo particular con el fin de satisfacer la valencia del mismo. Por ejemplo, el número de sustituyentes puede ser 1, 2, 3, 4, 5, 6 o 7.

[0135] "Mono-alquilamino" denota el grupo -NHR^c donde R^c es alquilo inferior. "Di-alquilamino" denota el grupo -NR^cR^d, donde R^c y R^d son independientemente alquilo inferior. "Cicloalquilamino" denota el grupo -NR^eR^f, donde R^e y R^f se combinan con el nitrógeno para formar un heterocicloalquilo de 5-7

miembros, donde el heterocicloalquilo puede contener un heteroátomo adicional dentro del anillo, tal como O, N, o S, y también puede sustituirse además con alquilo inferior. Ejemplos de heterocicloalquilo de 5-7 miembros incluyen, pero no se limitan a, piperidina, piperazina, 4-metilpiperazina, morfolina, y tiomorfolina. Se entiende que cuando el mono-alquilamino, di-alquilamino, o cicloalquilamino son sustituyentes en otras porciones, estas son químicamente factibles y se unen en cualquier átomo disponible para proporcionar un compuesto estable.

[0136] Como se usa en este documento "Grupo protector" se refiere a un grupo de átomos que, cuando se unen a un grupo reactivo en una molécula, enmascaran, reducen o evitan la reactividad. Ejemplos de grupos protectores pueden encontrarse en T.W. Greene and P.G. Wuts, PROTECTIVE GROUPS IN ORGANIC CHEMISTRY, (Wiley, 4th ed. 2006), Beaucage and Iyer, *Tetrahedron* 48:2223-2311 (1992), y Harrison and Harrison *et al.*, COMPENDIUM OF SYNTHETIC ORGANIC METHODS, Vols. 1-8 (John Wiley and Sons. 1971-1996). 1971-1996). Grupos protectores amino representativos incluyen formilo, acetilo, trifluoroacetilo, bencilo, benciloxicarbonilo (CBZ), *ter*-butoxicarbonilo (Boc), trimetil sililo (TMS), 2-trimetilsilil-etanosulfonilo (SES), tritilo y grupos tritilo sustituidos, aliloxicarbonilo, 9-fluorenilmetiloxicarbonilo (FMOC), nitro-veratriloxicarbonilo (NVOC), tri-isopropilsililo (TIPS), fenilsulfonilo y similares (véase también, Boyle, A. L. (Editor), CURRENT PROTOCOLS IN NUCLEIC ÁCIDO CHEMISTRY, John Wiley and Sons, New York,Volume 1, 2000).

[0137] Como se usa en este documento, los términos "tratar", "tratando", "terapia", "terapias", y términos similares se refieren a la administración de material, por ejemplo, uno cualquiera o más compuestos, como se describe en este documento, en una cantidad efectiva para evitar, aliviar, o mejorar uno o más síntomas de una enfermedad o padecimiento, es decir, indicación, y/o para prolongar la supervivencia del sujeto que se trata.

[0138] Como se utiliza en este documento, el término "enfermedad o padecimiento mediado por proteína cinasa Raf" se refiere a una enfermedad o padecimiento en el que la función biológica de una proteína cinasa Raf (también referida como Raf cinasa, o Raf), incluyendo cualquiera de una proteína cinasa A-Raf, proteína cinasa B-Raf o proteína cinasa c-Raf-1, o cualquier mutación de la misma, afecta el desarrollo, curso, y/o síntomas de la enfermedad o padecimiento, y/o en el que la modulación de Raf altera el desarrollo, curso, y/o síntomas de la enfermedad o padecimiento. La enfermedad o padecimiento mediado por Raf incluye una enfermedad o padecimiento para el cual la modulación de Raf proporciona un beneficio terapéutico, por ejemplo, en donde el tratamiento con inhibidores de Raf, incluyendo uno o más compuestos descritos en este documento, proporciona un beneficio terapéutico al sujeto que adolece o está en riesgo de la enfermedad o padecimiento.

[0139] Como se utiliza en este documento, el término "enfermedad o padecimiento mediado por proteína cinasa A-Raf", y similares se refieren a una enfermedad o padecimiento en el que la función biológica de una proteína cinasa A-Raf (también referida como cinasa A-Raf, o A-Raf), incluyendo cualquier mutación de la misma, afecta el desarrollo, curso, y/o síntomas de la enfermedad o condición, y/o en el que la modulación de A-Raf altera el desarrollo, curso, y/o síntomas de la enfermedad o padecimiento. La enfermedad o padecimiento mediado por A-Raf incluye una enfermedad o padecimiento para el cual la

inhibición de A-Raf proporciona un beneficio terapéutico, por ejemplo, en donde el tratamiento con un compuesto que inhibe A-Raf, incluyendo uno o más compuestos descritos en este documento, proporciona un beneficio terapéutico al sujeto que adolece o está en riesgo de la enfermedad o padecimiento.

[0140] Como se utiliza en este documento, el término "enfermedad o padecimiento mediado por proteína cinasa B-Raf", y similares se refieren a una enfermedad o padecimiento en el que la función biológica de una proteína cinasa B-Raf (también referida como cinasa B-Raf, o B-Raf), incluyendo cualquier mutación de la misma, afecta el desarrollo, curso, y/o síntomas de la enfermedad o condición, y/o en el que la modulación de B-Raf altera el desarrollo, curso, y/o síntomas de la enfermedad o padecimiento. La enfermedad o padecimiento mediado por B-Raf incluye una enfermedad o padecimiento para el cual la inhibición de B-Raf proporciona un beneficio terapéutico, por ejemplo, en donde el tratamiento con un compuesto que inhibe B-Raf, incluyendo uno o más compuestos descritos en este documento, proporciona un beneficio terapéutico al sujeto que adolece o está en riesgo de la enfermedad o padecimiento.

[0141] Como se utiliza en este documento, el término "enfermedad o padecimiento mediado por proteína cinasa mutante B-Raf V600E", y similares se refieren a una enfermedad o padecimiento en el que la función biológica de la proteína cinasa mutante B-Raf V600E (también referida como cinasa B-Raf V600E, o B-Raf V600E), incluyendo cualquier mutación de la misma, afecta el desarrollo, curso, y/o síntomas de la enfermedad o condición, y/o en el que la modulación de B-Raf V600E altera el desarrollo, curso, y/o síntomas de la enfermedad o padecimiento. La enfermedad o padecimiento mediado por B-Raf V600E incluye una enfermedad o padecimiento para el cual la inhibición de B-Raf V600E proporciona un beneficio terapéutico, por ejemplo, en donde el tratamiento con un compuesto que inhibe B-Raf V600E, incluyendo uno o más compuestos descritos en este documento, proporciona un beneficio terapéutico al sujeto que adolece o está en riesgo de la enfermedad o padecimiento.

[0142] Como se utiliza en este documento, el término "enfermedad o padecimiento mediado por proteína cinasa c-Raf-1", y similares se refieren a una enfermedad o padecimiento en el que la función biológica de una proteína cinasa c-Raf-1 (también referida como cinasa c-Raf-1, o c-Raf-1), incluyendo cualquier mutación de la misma, afecta el desarrollo, curso, y/o síntomas de la enfermedad o condición, y/o en el que la modulación de c-Raf-1 altera el desarrollo, curso, y/o síntomas de la enfermedad o padecimiento. La enfermedad o padecimiento mediado por c-Raf-1 incluye una enfermedad o padecimiento para el cual la inhibición de c-Raf-1 proporciona un beneficio terapéutico, por ejemplo, en donde el tratamiento con un compuesto que inhibe c-Raf-1, incluyendo uno o más compuestos descritos en este documento, proporciona un beneficio terapéutico al sujeto que adolece o está en riesgo de la enfermedad o padecimiento.

[0143] Como se utiliza en este documento, el término "inhibidor de Raf" se refiere a un compuesto que inhibe por lo menos una de A-Raf, B-Raf, c-Raf-1, o cualquier mutación de las mismas, es decir, un compuesto que tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente

aceptado de actividad de cinasa Raf. Tales compuestos preferiblemente, pero no necesariamente, son selectivos con respecto a otras proteína cinasas, es decir, cuando se comparan con otra proteína cinasa, la IC_{50} para la otra cinasa dividida entre la IC_{50} para la Raf cinasa es >10, también >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. Preferiblemente, los compuestos son selectivos en relación con otras proteína cinasas incluyendo, pero sin limitarse a, CSK, cinasa del receptor de insulina, AMPK, PDGFR o VEGFR.

[0144] Como se utiliza en este documento, el término "inhibidor de c-Raf-1" se refiere a un compuesto que inhibe la proteína cinasa c-Raf-1, es decir, un compuesto que tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa c-Raf-1. Tales compuestos son efectivos para tratar una enfermedad o padecimiento que está mediado por c-Raf-1. Tales compuestos preferiblemente, pero no necesariamente, son selectivos con respecto a otras proteína cinasas, es decir, cuando se comparan con otra proteína cinasa, la IC_{50} para la otra cinasa dividida entre la IC_{50} para la c-Raf-1 cinasa es >10, también >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. Preferiblemente, los compuestos son selectivos en relación con otras proteína cinasas incluyendo, pero sin limitarse a, CSK, cinasa del receptor de insulina, AMPK, PDGFR o VEGFR. Tales compuestos preferiblemente, pero no necesariamente, también son selectivos con respecto a otras proteína cinasas Raf, es decir, cuando se comparan con otra proteína cinasa Raf, la IC_{50} para la otra Raf cinasa dividida entre la IC_{50} para la c-Raf-1 cinasa es >10, también >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. Preferiblemente tales compuestos son por lo menos selectivos en relación con B-Raf y B-Raf V600E. Aunque se entiende que un inhibidor de c-Raf-1 puede utilizarse para tratar cualquier enfermedad o padecimiento mediado por c-Raf-1, la inhibición de c-Raf-1, preferiblemente la inhibición selectiva de c-Raf-1, proporciona efectos benéficos para tratar el dolor agudo, dolor crónico, y enfermedad renal poliquística.

[0145] Como se utiliza en este documento, el término "inhibidor de B-Raf V600E" se refiere a un compuesto que inhibe la proteína cinasa mutante B-Raf V600E, es decir, un compuesto que tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa B-Raf V600E. Tales compuestos son efectivos para tratar una enfermedad o padecimiento que está mediado por B-Raf V600E. Tales compuestos preferiblemente, pero no necesariamente, son selectivos con respecto a otras proteína cinasas, es decir, cuando se comparan con otra proteína cinasa, la IC_{50} para la otra cinasa dividida entre la IC_{50} para la B-Raf V600E cinasa es >10, también >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. Preferiblemente, los compuestos son selectivos en relación con otras proteína cinasas incluyendo, pero sin limitarse a, CSK, cinasa del receptor de insulina, AMPK, PDGFR o VEGFR. Tales compuestos preferiblemente, pero no necesariamente, también son selectivos con respecto a otras proteína cinasas Raf, es decir, cuando se comparan con otra proteína cinasa Raf, la IC_{50} para la otra Raf cinasa dividida entre la IC_{50} para la B-Raf V600E cinasa es >10, también >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. Aunque se entiende que un

inhibidor de B-Raf V600E puede utilizarse para tratar cualquier enfermedad o padecimiento mediado por B-Raf V600E, la inhibición de B-Raf V600E proporciona efectos benéficos para tratar melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, cáncer colorrectal, cáncer de tiroides, cáncer de pulmón, cáncer ovárico, cáncer de próstata, cáncer hepático, cáncer de vesícula biliar, tumores de estroma gastrointestinal, cáncer del tracto biliar, y colangiocarcinoma.

[0146] Como se utiliza en este documento, el término "pan inhibidor de Raf" se refiere a un compuesto que inhibe por lo menos cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E, es decir, un compuesto que tiene una IC_{50} de menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa B-Raf, y que tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo comparable generalmente aceptado de actividad de cinasa c-Raf-1, y que tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo comparable generalmente aceptado de actividad de cinasa B-Raf V600E. El pan inhibidor de Raf puede ser, pero no necesariamente, aproximadamente igual de potente sobre cada una de B-Raf, c-Raf-1 y B-Raf V600E. Los compuestos se consideran aproximadamente igual de potentes sobre cada una de B-Raf V600E, B-Raf y c-Raf-1 si la relación de IC_{50} para cualquiera de B-Raf V600E, B-Raf y c-Raf-1 dividida entre la IC_{50} para cualquier otra de B-Raf V600E, B-Raf y c-Raf-1 (por ejemplo, IC_{50} de B-Raf dividida entre IC_{50} de B-Raf V600E) se encuentra en el intervalo de 10 a 0.1, también 5 a 0.2. Tales compuestos preferiblemente, pero no necesariamente, son selectivos con respecto a otras proteína cinasas, es decir, cuando se comparan con otra proteína cinasa, la IC_{50} para la otra cinasa dividida entre la IC_{50} para cualquiera de B-Raf, c-Raf-1 o B-Raf V600E es >10, también >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. Preferiblemente, los compuestos son selectivos en relación con otras proteína cinasas incluyendo, pero sin limitarse a, CSK, cinasa del receptor de insulina, AMPK, PDGFR o VEGFR. Aunque se entiende que un pan inhibidor de Raf puede utilizarse para tratar cualquier enfermedad o padecimiento mediado por las cinasas B-Raf, c-Raf-1 o B-Raf V600E, la inhibición de cada una de B-Raf, c-Raf-1 y B-Raf V600E proporciona efectos benéficos para tratar cánceres, en particular cánceres que tienen una mutación en la ruta de Ras, incluyendo, pero sin limitarse a, melanoma, glioma, glioblastoma, astrocitoma pilocítico, cáncer de hígado, cáncer del tracto biliar, colangiocarcinoma, cáncer colorrectal, cáncer de pulmón, cáncer de vejiga, cáncer de vesícula biliar, cáncer de mama, cáncer pancreático, cáncer de tiroides, cáncer de riñón, cáncer ovárico, cáncer adrenocortical, cáncer de próstata, tumores de estroma gastrointestinal, cáncer de tiroides medular, angiogénesis tumoral, leucemia mieloide aguda, leucemia mielomonocítica crónica, leucemia linfoblástica aguda de la niñez, leucemia de células plasmáticas, y mieloma múltiple. Tales compuestos también son benéficos para tratar cánceres mediados por B-Raf V600E que se vuelven resistentes a los inhibidores selectivos de B-Raf V600E.

[0147] Como se utiliza en este documento, el término "inhibidor de la actividad de Ras" se refiere a un compuesto que inhibe la proliferación de una línea celular mutante de Ras; es decir, un compuesto que inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 1 μM, 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM. En algunas

modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 1 μM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 100 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 50 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 20 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 10 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 5 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 1 nM. En algunas modalidades la línea celular mutante de Ras es una línea celular mutante en N-Ras, una línea celular mutante en K-Ras, o una línea celular mutante en H-Ras. En diversas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de N-Ras con una IC_{50} de menos de 1 μM, 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de N-Ras con una IC_{50} de menos de 1 μM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de N-Ras con una IC_{50} de menos de 100 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de N-Ras con una IC_{50} de menos de 50 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de N-Ras con una IC_{50} de menos de 20 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de N-Ras con una IC_{50} de menos de 10 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de N-Ras con una IC_{50} de menos de 5 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de N-Ras con una IC_{50} de menos de 1 nM. En ciertas modalidades, la línea celular mutante en N-Ras es una o más líneas celulares seleccionadas del grupo que consiste en M244, M202, M207, SK-MEL-2, IPC-298, S`117, M296, SK-MEL-30, SK-MEL-173, y HL-60. En algunas modalidades, la línea celular mutante en N-Ras es una o más líneas celulares seleccionadas del grupo que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de Ras seleccionada del grupo que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298 con una IC_{50} de menos de 1 μM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de Ras seleccionada del grupo que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298 con una IC_{50} de menos de 100 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de Ras seleccionada del grupo que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298 con una IC_{50} de menos de 50 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de Ras seleccionada del grupo que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298 con una IC_{50} de menos de 20 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de Ras seleccionada del grupo que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298 con

una IC_{50} de menos de 10 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de Ras seleccionada del grupo que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298 con una IC_{50} de menos de 5 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de una línea celular mutante de Ras seleccionada del grupo que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298 con una IC_{50} de menos de 1 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de células IPC298 de Ras con una IC_{50} de menos de 1 μM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de células IPC298 de Ras con una IC_{50} de menos de 100 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de células IPC298 de Ras con una IC_{50} de menos de 50 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de células IPC298 de Ras con una IC_{50} de menos de 20 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de células IPC298 de Ras con una IC_{50} de menos de 10 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de células IPC298 de Ras con una IC_{50} de menos de 5 nM. En algunas modalidades, un inhibidor de la actividad de Ras inhibe la proliferación de células IPC298 de Ras con una IC_{50} de menos de 1 nM.

[0148] Como se utiliza en este documento, el término "forma sólida" se refiere a una preparación sólida (es decir, una preparación que no es gas ni líquido) de un compuesto farmacéuticamente activo que es adecuado para la administración a un sujeto animal destinado, para propósitos terapéuticos. La forma sólida incluye cualquier complejo, tal como una sal, co-cristal o un complejo amorfo, así como cualquier polimorfo del compuesto. La forma sólida puede ser sustancialmente cristalina, semi-cristalina o sustancialmente amorfa. La forma sólida puede administrarse directamente o puede utilizarse en la preparación de una composición adecuada que tiene propiedades farmacéuticas mejoradas. Por ejemplo, la forma sólida puede utilizarse en una formulación que comprende por lo menos un portador o excipiente farmacéuticamente aceptable.

[0149] Como se utiliza en este documento, el término material "sustancialmente cristalino" abarca material que tiene más de aproximadamente 90% de cristalinidad; y material "cristalino" abarca material que tiene más de aproximadamente 98% de cristalinidad.

[0150] Como se utiliza en este documento, el término material "sustancialmente amorfo" abarca material que tiene no más de aproximadamente 10% de cristalinidad; y material "amorfo" abarca material que tiene no más de aproximadamente 2% de cristalinidad.

[0151] Como se utiliza en este documento, el término material "semi-cristalino" abarca material que tiene más de 10% de cristalinidad, pero no más de 90% de cristalinidad; el material preferiblemente "semi-cristalino" abarca material que tiene más de 20% de cristalinidad, pero no más de 80% de cristalinidad. En un aspecto de la presente invención, puede prepararse una mezcla de formas sólidas de un compuesto, por ejemplo, una mezcla de formas sólidas amorfas y cristalinas, por ejemplo, para proporcionar una forma sólida "semi-cristalina". Tal forma sólida "semi-cristalina" puede prepararse por métodos conocidos en la técnica, por ejemplo, al mezclar una forma sólida amorfa con una forma sólida cristalina en la proporción deseada. En algunos casos, un compuesto mezclado con un ácido o base forma un

complejo amorfo; un sólido semi-cristalino puede prepararse al emplear una cantidad de componente compuesto que excede la estequiometría del compuesto y el ácido o la base en el complejo amorfo, con lo cual se tiene como resultado una cantidad del complejo amorfo que se basa en la estequiometría del mismo, con el compuesto en exceso en una forma cristalina. La cantidad de compuesto en exceso utilizado en la preparación del complejo puede ajustarse para proporcionar la relación deseada de complejo amorfo a compuesto cristalino en la mezcla resultante de formas sólidas. Por ejemplo, en casos donde el complejo amorfo de ácido o base y compuesto tiene una estequiometría 1:1, preparar dicho complejo con una relación molar 2:1 de compuesto a ácido o base, tendrá como resultado una forma sólida de 50% de complejo amorfo y 50% de compuesto cristalino. Tal mezcla de formas sólidas puede ser beneficiosa como un producto farmacológico, por ejemplo, al proporcionar un componente amorfo que tiene propiedades biofarmacéuticas mejoradas en conjunto con el componente cristalino. El componente amorfo podría estar más fácilmente biodisponible, mientras el componente cristalino tendría una biodisponibilidad retardada. Tal mezcla puede proporcionar una exposición tanto rápida como prolongada al compuesto activo.

[0152] Como se utiliza en este documento, el término "complejo" se refiere a una combinación de un compuesto farmacéuticamente activo y una especie molecular adicional que forma o produce una nueva especie química en una forma sólida. En algunos casos, el complejo puede ser una sal, es decir, donde la especie molecular adicional proporciona un contra ión ácido/base a un grupo ácido/base del compuesto, lo que tiene como resultado una interacción ácido:base que forma una sal típica. Aunque tales formas de sal de manera típica son sustancialmente cristalinas, también pueden ser formas parcialmente cristalinas, sustancialmente amorfas o amorfas. En algunos casos, la especie molecular adicional, en combinación con el compuesto farmacéuticamente activo, forma un co-cristal no salino, es decir, el compuesto y la especie molecular no interactúan a manera de una interacción típica ácido:base, sino todavía forman una estructura sustancialmente cristalina. Los co-cristales también pueden formarse a partir de una sal del compuesto y una especie molecular adicional. En algunos casos, el complejo es un complejo sustancialmente amorfo, que puede contener interacciones ácido:base de tipo sal que no forman cristales típicos de sal, pero forman, en lugar de ello, un sólido sustancialmente amorfo, es decir, un sólido cuyo patrón de difracción en polvo de rayos X no exhibe picos agudos (por ejemplo, exhibe un halo amorfo).

[0153] Como se utiliza en este documento, el término "estequiometría" se refiere a la relación molar de una combinación de dos o más componentes, por ejemplo, la relación molar de ácido o base a compuesto que forma un complejo amorfo. Por ejemplo, una mezcla 1:1 de ácido o base con compuesto (es decir, 1 mol de ácido o base por mol de compuesto), que tiene como resultado una forma sólida amorfa, tiene una estequiometría 1:1.

[0154] Como se utiliza en este documento, el término "composición" se refiere a una preparación farmacéutica adecuada para su administración a un sujeto destinado, para propósitos terapéuticos, que contiene por lo menos un compuesto farmacéuticamente activo, incluyendo cualquier forma sólida del mismo. La composición puede incluir por lo menos un componente farmacéuticamente aceptable para proporcionar una formulación mejorada del compuesto, tal como un portador o excipiente conveniente.

[0155] Como se usa en este documento, el término "sujeto" se refiere a un organismo viviente que se trata con los compuestos como se describe en este documento, incluyendo, pero sin limitarse a, cualquier mamífero, tal como un humano, otros primates, animales para deporte, animales de interés comercial tal como ganado vacuno, animales de granja tales como caballos, o mascotas tales como perros y gatos.

[0156] Como se usa en este documento, el término "propiedades biofarmacéuticas" se refiere a la acción farmacocinética de un compuesto o complejo de la presente invención, incluyendo la disolución, absorción y distribución del compuesto en la administración a un sujeto. Como tales, ciertas formas sólidas de los compuestos de la invención, tales como complejos amorfos de los compuestos de la invención, pretenden proporcionar una disolución y absorción mejoradas del compuesto activo, que se refleja típicamente en una C_{max} mejorada (es decir, la concentración máxima alcanzada en el plasma después de la administración del fármaco) y AUC mejorada (es decir, área bajo la curva de la concentración plasmática del fármaco vs. tiempo después de la administración del fármaco).

[0157] El término "farmacéuticamente aceptable" señala que el material indicado no tiene propiedades que podrían ocasionar que un médico razonablemente prudente evite la administración del material a un paciente, tomando en consideración la enfermedad o padecimientos que se tratarán y la respectiva ruta de administración. Por ejemplo, se requiere comúnmente que tal material sea en esencia estéril, por ejemplo, para los inyectables.

[0158] En el contexto presente, el término "terapéuticamente efectivo" o "cantidad efectiva" indica que los materiales o la cantidad de material son efectivos prevenir, aliviar, o mejorar uno o más síntomas de una enfermedad o padecimiento médico, y/o para prolongar la supervivencia del sujeto que se trata.

[0159] En el contexto presente, los términos "sinérgicamente efectivo" o "efecto sinérgico" indican que dos o más compuestos que son terapéuticamente efectivos, cuando se usan en combinación, proporcionan efectos terapéuticos mejorados superiores al efecto aditivo que podría esperarse con base en el efecto de cada compuesto utilizado por sí mismo.

[0160] Por "analizar" se quiere decir la creación de condiciones experimentales y la acumulación de datos respecto a un resultado particular de las condiciones experimentales. Por ejemplo, pueden probarse enzimas con base en su capacidad para actuar sobre un sustrato detectable. Un compuesto puede probarse con base en su capacidad para unirse a una molécula o moléculas objetivo particulares.

[0161] Como se utiliza en este documento, el término "modular" o "modulan" se refiere a un efecto de alterar una actividad biológica (es decir, incrementar o disminuir la actividad), especialmente una actividad biológica asociada con una biomolécula particular tal como una proteína cinasa. Por ejemplo, un inhibidor de una biomolécula particular modula la actividad de esa biomolécula, *por ejemplo*, una enzima, al reducir la actividad de la biomolécula, tal como una enzima. Tal actividad típicamente se indica en cuanto a una concentración inhibitoria (IC_{50}) del compuesto para un inhibidor con respecto, por ejemplo, a una enzima.

[0162] En el contexto del uso, prueba, o selección de los compuestos que son o pueden ser moduladores, el término "contactar" significa que se provoca que el o los compuestos estén en suficiente proximidad a una molécula particular, complejo, célula, tejido, organismo, u otro material especificado que pueden ocurrir interacciones potenciales de unión y/o la reacción química entre el compuesto y otro material especificado.

[0163] "Dolor" o un "padecimiento doloroso" puede ser dolor agudo y/o crónico, incluyendo, sin limitación, aracnoiditis; artritis (por ejemplo, osteoartritis, artritis reumatoide, espondilitis anquilosante, gota); dolor de espalda (por ejemplo, ciática, disco roto, espondilolistesis, radiculopatía); dolor por quemadura; dolor por cáncer; dismenorrea; jaquecas (por ejemplo, migraña, jaquecas por grupo, jaquecas por tensión); dolor de cabeza y facial (por ejemplo, neuralgia craniana, neuralgia del trigémino); hiperalgesia; hiperpatía; dolor inflamatorio (por ejemplo, dolor asociado con síndrome del intestino irritable, enfermedad intestinal inflamatoria, colitis ulcerativa, enfermedad de Crohn, cistitis, dolor de infección bacteriana, fúngica o viral); formación de tejido queloide o de cicatrización; dolor de labor o parto; dolor muscular (por ejemplo, como resultado de polimiositis, dermatomiositis, miositis por cuerpos de inclusión, lesión repetitiva por estrés (por ejemplo, calambre del escritor, síndrome del túnel carpiano, tendonitis, tenosinovitis)); síndromes de dolor miofascial (por ejemplo, fibromialgia); dolor neuropático (por ejemplo, diabética neuropatía, causalgia, neuropatía por atrapamiento, avulsión del plexo braquial, neuralgia occipital, gota, síndrome de distrofia del reflejo simpático, extremidad fantasma o dolor pos-amputación, neuralgia posherpética, síndrome de dolor central, o dolor de nervios que resulta de trauma (por ejemplo, lesión de nervios), enfermedad (por ejemplo, diabetes, esclerosis múltiple, Síndrome de Guillan-Barre, miastenia grave, enfermedades neurodegenerativas tales como enfermedad de Parkinson, enfermedad de Alzheimer, esclerosis lateral amiotrófica, o tratamiento de cáncer); dolor asociado con trastornos de piel (por ejemplo, zoster, herpes simple, tumores de piel, quistes, neurofibromatosis); lesiones deportivas (por ejemplo, cortes, torceduras, tirones, contusiones, dislocaciones, fracturas, médula espinal, cabeza); estenosis espinal; dolor quirúrgico; alodinia táctil; trastornos temporomandibulares; enfermedad o lesión vascular (por ejemplo, vasculitis, enfermedad de arterias coronarias, lesión por reperfusión (por ejemplo, después de isquemia, apoplejía, o de infartos de miocardio)); otro dolor específico de órganos o tejidos (por ejemplo, dolor ocular, dolor córneo, dolor óseo, dolor de corazón, dolor visceral (por ejemplo, riñón, vesícula biliar, gastrointestinal), dolor de articulaciones, dolor dental, hipersensibilidad pélvica, dolor pélvico, cólico renal, incontinencia urinaria); otro dolor asociado a enfermedad (por ejemplo, anemia de células falciformes, SIDA, herpes zoster, psoriasis, endometriosis, asma, enfermedad pulmonar obstructiva crónica (COPD), silicosis, sarcoidosis pulmonar, esofagitis, acedía, trastorno por reflujo gastroesofágico, úlceras de estómago y duodenal, dispepsia funcional, enfermedad de resorción ósea, osteoporosis, malaria cerebral, meningitis bacteriana); o dolor debido a rechazo injerto v. huésped o rechazos de aloinjertos.

Objetivos cinasa e indicaciones de la invención

[0164] Las proteína cinasas juegan papeles clave en propagar señales bioquímicas en diversas rutas biológicas. Más de 500 cinasas se han descrito, y cinasas específicas se han implicado en una amplia variedad de enfermedades o padecimientos (es decir, indicaciones), incluyendo por ejemplo, sin

limitación, cáncer, enfermedad cardiovascular, enfermedad inflamatoria, enfermedad neurológica, y otras enfermedades. Como tales, las cinasas representan importantes puntos de control para la intervención terapéutica con pequeñas moléculas. Proteína cinasas objetivo específicas contempladas por la presente invención se describen en la técnica, incluyendo, sin limitación, proteína cinasas como se describe en la Solicitud de Patente de E.U. Número de Serie 11/473,347 (véase también, publicación PCT WO2007002433), cuya descripción se incorpora por la presente para referencia dado que se relaciona con tales objetivos de cinasas, así como lo siguiente:

[0165] **A-Raf:** Cinasa objetivo A-Raf (es decir, homólogo 1 del oncogen viral v-raf de sarcoma murino 3611) es una serina/treonina cinasa de67.6 kDa codificada por el cromosoma Xp11.4-p11.2 (símbolo: ARAF). La proteína madura comprende RBD (es decir, dominio de unión a Ras) y dominio de dedos de zinc tipo forbol-éster/DAG y se implica en la transducción de señales mitogénicas de la membrana celular al núcleo. Los inhibidores de A-Raf pueden ser útiles para tratar enfermedades neurológicas tales como demencia vascular, lesión en cabeza, lesión en médula espinal, enfermedad de Alzheimer (AD), enfermedad de Parkinson; enfermedades neoplásicas incluyendo, pero sin limitarse a, melanoma, glioma, sarcoma, carcinoma (por ejemplo, colorectal, de pulmón, de mama, pancreático, tiroideo, renal, ovárico), linfoma (por ejemplo, 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 asociadas con regeneración o degeneración muscular, incluyendo, pero sin limitarse a, restenosis vascular, sarcopenia, distrofias musculares (incluyendo, pero sin limitarse a, Distrofias de Duchenne, Becker, Emery-Dreifuss, de Cintura Pélvica, Facioescapulohumeral, Miotónica, Oculofaríngea, Distal y Muscular Congénita), enfermedades de neuronas motoras (incluyendo, pero sin limitarse a, esclerosis lateral amiotrófica, atrofia muscular espinal progresiva infantil, atrofia muscular espinal intermedia, atrofia muscular espinal juvenil, atrofia muscular bulbar espinal, y atrofia muscular espinal adulta), miopatías inflamatorias (incluyendo, pero sin limitarse a, dermatomiositis, polimiositis, y miositis por cuerpos de inclusión), enfermedades de la placa neuromuscular (incluyendo, pero sin limitarse a, miastenia grave, síndrome de Lambert-Eaton, y síndrome miasténico congénito), miopatías debido a anormalidades endocrinas (incluyendo, pero sin limitarse a, miopatía hipertiroidea y miopatía hipotiroidea) enfermedades de nervios periféricos (incluyendo, pero sin limitarse a, enfermedad de Charcot Marie Tooth, enfermedad de Dejerine-Sottas, y ataxia de Friedreich), otras miopatías (incluyendo, pero sin limitarse a, miotonía congénita, paramiotonía congénita, enfermedad de núcleo central, miopatía nemalínica, miopatía miotubular, y parálisis periódica), y enfermedades metabólicas de músculo (incluyendo, pero sin limitarse a, deficiencia de fosforilasa, deficiencia de maltasa ácida, deficiencia de fosfofructocinasa, deficiencia de enzima de desconexión, miopatía mitocondrial, deficiencia de carnitina, deficiencia de carnitina palmatilo transferasa, deficiencia de fosfoglicerato cinasa, deficiencia de fosfoglicerato mutasa, deficiencia de lactato deshidrogenasa, y deficiencia de mioadenilato desaminasa).

[0166] **B-Raf:** Cinasa objetivo B-Raf (es decir, homólogo B1 del oncogen de sarcoma viral murino v-raf) es una serina/treonina cinasa de 84.4 kDa codificada por el cromosoma 7q34 (símbolo: BRAF). La proteína madura comprende los dominios RBD (es decir, dominio de unión a Ras), C1 (es decir, proteína cinasa C región conservada 1) y STK (es decir, serina/treonina cinasa).

[0167] La cinasa objetivo B-Raf se implica en la transducción de señales mitogénicas de la membrana celular al núcleo y puede jugar un papel en las respuestas postsinápticas de neuronas del hipocampo. Como tales, los genes de la familia RAF codifican cinasas que se regulan por Ras y median respuestas celulares a señales de crecimiento. De hecho, la cinasa B-Raf es un componente clave de la ruta de señalización de cinasas RAS->Raf-> MEK->ERK/MAP, que juega un papel fundamental en la regulación de crecimiento, división y proliferación celular, y, cuando está constitutivamente activada, ocasiona tumorigénesis. Entre varias isoformas de cinasa Raf, la tipo B, o B-Raf, es el activador más fuerte de la señalización de MAP cinasas corriente abajo.

[0168] El gen BRAF se muta frecuentemente en una diversidad de tumores humanos, especialmente en melanoma maligno y carcinoma de colon. La mutación reportada más común fue una transversión sin sentido timina (T) a adenina (A), en el nucleótido 1796 (T1796A; el cambio de aminoácido en la proteína B-Raf es Val<600> a Glu<600>) observada en 80% de los tumores de melanoma maligno. El análisis funcional revela que esta transversión es la única mutación detectada que ocasiona activación constitutiva de actividad de cinasa B-Raf, independiente de la activación de RAS, al convertir B-Raf en una proteína transformante dominante. Con base en lo precedente, los tumores humanos desarrollan resistencia a inhibidores de cinasas al mutar un aminoácido específico en el dominio catalítico como el "portero". (Balak, et. al., Clin Cancer Res. 2006, 12:6494-501). La mutación de Thr-529 en BRAF a Ile se anticipa de esta manera como un mecanismo de resistencia a inhibidores de BRAF, y esto puede visualizarse como una transición en el codón 529 de ACC a ATC.

[0169] Niihori et al. reportan que en 43 individuos con síndrome cardio-facio-cutáneo (CFC), identificaron dos mutaciones heterocigóticas KRAS en tres individuos y ocho mutaciones BRAF en 16 individuos, sugiriendo que la ausencia de regulación 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 cánceres asociados con la falta de regulación de la ruta RAS-RAF-ERK, tales como cánceres que tienen mutaciones B-Raf V600E o mutaciones NRAS, pueden tratarse con los inhibidores de Raf cinasas, tales como los Pan inhibidores de Raf cinasas como se describe en este documento. La capacidad de estos compuestos para inhibir múltiples objetivos Raf cinasas, incluyendo c-Raf-1, B-Raf, y B-Raf V600E, proporciona beneficios adicionales para inhibir mutaciones activadoras en esta ruta, con tales cánceres con menor probabilidad de desarrollar resistencia a tales inhibidores dado que se orientan a varios puntos en la ruta. Los pan inhibidores de Raf cinasas, como se describe en este documento, pueden ser útiles para tratar una diversidad de cánceres, incluyendo, pero sin limitarse a, melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, carcinoma (por ejemplo, gastrointestinal, hígado, tracto biliar, ducto biliar (colangiocarcinoma), colorrectal, pulmón, cerebro, vejiga, vesícula biliar, mama, pancreático, tiroides, riñón, ovárico, adrenocortical, próstata), tumores de estroma gastrointestinal, cáncer de tiroides medular, angiogénesis tumoral, leucemia mieloide aguda, leucemia mielomonocítica crónica, leucemia linfoblástica aguda de la niñez, 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:** Cinasa objetivo c-Raf-1 (es decir, homólogo 1 del oncogen v-raf de sarcoma viral murino) es una STK de 73.0 kDa codificada por el cromosoma 3p25 (símbolo: RAF1). c-Raf-1 puede orientarse a la mitocondria por BCL2 (es decir, oncogen 2 de leucemia de células B) que es un regulador de muerte celular apoptótica. El c-Raf-1 activo mejora la resistencia a apoptosis mediada por BCL2, y c-Raf-1 fosforila BAD (es decir, proteína de unión a BCL2). c-Raf-1 se implica en carcinomas, incluyendo carcinoma colorectal, ovárico, de pulmón y de células renales. C-Raf-1 también se implica como un importante mediador de angiogénesis tumoral (Hood, J.D. et al., 2002, Science 296, 2404). Los inhibidores de C-Raf-1 también pueden ser útiles para el tratamiento de leucemia mieloide aguda y síndromes mielodisplásicos (Crump, Curr Pharm Des 2002, 8(25):2243-8). Los activadores de Raf-1 pueden ser útiles como tratamiento para tumores neuroendocrinos, tal como cáncer de tiroides medular, carcinoide, cáncer de pulmón de células pequeñas y feocromocitoma (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 para tratar enfermedades o padecimientos mediados por A-Raf, mediados por B-Raf o mediados por c-Raf-1, seleccionados del grupo que consiste en enfermedades neurológicas, incluyendo, pero sin limitarse a, demencia vascular, lesión en cabeza, lesión en médula espinal, enfermedad de Alzheimer (AD), enfermedad de Parkinson, ataques y epilepsia; enfermedades neoplásicas incluyendo, pero sin limitarse a, melanoma, glioma, sarcoma, carcinoma (por ejemplo, gastrointestinal, de hígado, conducto biliar (colangiocarcinoma), colorectal, pulmón, mama, pancreático, tiroideo, renal, ovárico, próstata), linfoma (por ejemplo, linfoma histiocítico) neurofibromatosis, leucemia mieloide aguda, síndrome mielodisplásico, leucemia, angiogénesis tumoral, tumores neuroendocrinos tales como cáncer de tiroides medular, carcinoide, cáncer de pulmón de células pequeñas, sarcoma de Kaposi, y feocromocitoma; dolor de origen neuropático o inflamatorio, incluyendo, pero sin limitarse a, dolor agudo, dolor crónico, dolor relacionado con cáncer, y migraña; enfermedades cardiovasculares incluyendo, pero sin limitarse a, falla cardiaca, apoplejía isquémica, hipertrofia cardiaca, trombosis (por ejemplo, síndromes de microangiopatía trombótica), ateroesclerosis, y lesión por reperfusión; inflamación y/o proliferación incluyendo, pero sin limitarse a, psoriasis, eczema, artritis y enfermedades y padecimientos autoinmunes, osteoartritis, endometriosis, cicatrización, restenosis vascular, trastornos fibróticos, artritis reumatoide, enfermedad intestinal inflamatoria (IBD); enfermedades por inmunodeficiencias, incluyendo, pero sin limitarse a, rechazo de transplantes de órganos, enfermedad injerto versus huésped, y sarcoma de Kaposi asociado con HIV; enfermedades renales, quísticas, o prostáticas, incluyendo, pero sin limitarse a, nefropatía diabética, enfermedad renal poliquística, nefroesclerosis, glomerulonefritis, hiperplasia de próstata, enfermedad de hígado poliquístico, esclerosis tuberosa, enfermedad de Von Hippel Lindau, enfermedad renal medular quística, nefronoftisis, y fibrosis quística; trastornos metabólicos, incluyendo, pero sin limitarse a, obesidad; infección, incluyendo, pero sin limitarse a, Helicobacter pylori, virus de Hepatitis e Influenza, fiebre, HIV, y septicemia; enfermedades pulmonares incluyendo, pero sin limitarse a, enfermedad pulmonar obstructiva crónica (COPD) y síndrome de insuficiencia respiratoria aguda (ARDS); enfermedades genéticas del desarrollo, incluyendo, pero sin limitarse a, síndrome de Noonan, síndrome de Costello, (síndrome faciocutaneoesquelético), síndrome LEOPARD, síndrome cardio-faciocutáneo (CFC), y anormalidades del síndrome de crestas neurales que provocan enfermedades cardiovasculares,

esqueléticas, intestinales, de piel, cabello y endocrinas; y enfermedades asociadas con regeneración o degeneración muscular, incluyendo, pero sin limitarse a, sarcopenia, distrofias musculares (incluyendo, pero sin limitarse a, Distrofias de Duchenne, Becker, Emery-Dreifuss, de Cintura Pélvica, Facioescapulohumeral, Miotónica, Oculofaríngea, Distal y Muscular Congénita), enfermedades de neuronas motoras (incluyendo, pero sin limitarse a, esclerosis lateral amiotrófica, atrofia muscular espinal progresiva infantil, atrofia muscular espinal intermedia, atrofia muscular espinal juvenil, atrofia muscular bulbar espinal, y atrofia muscular espinal adulta), miopatías inflamatorias (incluyendo, pero sin limitarse a, dermatomiositis, polimiositis, y miositis por cuerpos de inclusión), enfermedades de la placa neuromuscular (incluyendo, pero sin limitarse a, miastenia grave, síndrome de Lambert-Eaton, y síndrome miasténico congénito), miopatías debido a anormalidades endocrinas (incluyendo, pero sin limitarse a, miopatía hipertiroidea y miopatía hipotiroidea) enfermedades de nervios periféricos (incluyendo, pero sin limitarse a, enfermedad de Charcot Marie Tooth, enfermedad de Dejerine-Sottas, y ataxia de Friedreich), otras miopatías (incluyendo, pero sin limitarse a, miotonía congénita, paramiotonía congénita, enfermedad de núcleo central, miopatía nemalínica, miopatía miotubular, y parálisis periódica), y enfermedades metabólicas de músculo (incluyendo, pero sin limitarse a, deficiencia de fosforilasa, deficiencia de maltasa ácida, deficiencia de fosfofructocinasa, deficiencia de enzima de desconexión, miopatía mitocondrial, deficiencia de carnitina, deficiencia de carnitina palmatilo transferasa, deficiencia de fosfoglicerato cinasa, deficiencia de fosfoglicerato mutasa, deficiencia de lactato deshidrogenasa, y deficiencia de mioadenilato desaminasa).

Ensayos de Actividad Cinasa

[0173] Una serie de diferentes ensayos para actividad de cinasa puede utilizarse para probar los moduladores activos y/o determinar especificidad de un modulador para una cinasa particular o grupo de cinasas. Además del ensayo mencionado en los Ejemplos a continuación, un experto en la técnica sabrá de otros ensayos que pueden utilizarse y puede modificar un ensayo para una aplicación particular. Por ejemplo, numerosos artículos concernientes a cinasas describen ensayos que pueden usarse.

[0174] Ensayos alternativos adicionales pueden emplear determinaciones de unión. **Por ejemplo, esta clase de ensayo puede formatearse en un formato de transferencia de energía por resonancia de fluorescencia (FRET), o usando un formato AlfaScreen (*e*nsayo *h*omogéneo de *p*roximidad *l*uminiscente *a*mplificada) al variar los reactivos donador y aceptor que se unen a estreptavidina o el anticuerpo específico de fósforo.**

Técnicas de síntesis orgánica

[0175] En el arte existe una amplia variedad de técnicas de síntesis orgánica para facilitar la construcción de moduladores potenciales. Muchos de estos métodos de síntesis orgánica se describen con todo detalle en fuentes estándar de referencia utilizadas por los expertos en la técnica. Un ejemplo de tal referencia es March, 1994, Advanced Organic Chemistry; Reactions, Mechanisms and Structure, New York, McGraw Hill. De esta manera, las técnicas útiles para sintetizar un modulador potencial de la función de cinasa se encuentran fácilmente disponibles para los expertos en la técnica de síntesis química orgánica.

Formas o derivados de compuestos alternativos

[0176] Los compuestos contemplados en este documento se describen con referencia tanto a fórmulas genéricas como compuestos específicos. Además, los compuestos de la invención pueden existir en una serie de formas o derivados diferentes, todos dentro del alcance de la presente invención. Las formas o derivados alternativos incluyen, por ejemplo, (a) profármacos, y metabolitos activos (b) tautómeros, isómeros (incluyendo estereoisómeros y regioisómeros), y mezclas racémicas (c) sales farmacéuticamente aceptables y (d) formas sólidas, incluyendo diferentes formas cristalinas, sólidos polimórficos o amorfos, incluyendo hidratos y solvatos de los mismos, y otras formas.

(a) Profármacos y metabolitos

[0177] Además de las presentes fórmulas y compuestos descritos en este documento, la invención también incluye profármacos (generalmente profármacos farmacéuticamente aceptables), derivados metabólicos activos (metabolitos activos), y sus sales farmacéuticamente aceptables.

[0178] Los profármacos son compuestos o sales farmacéuticamente aceptables de los mismos que, cuando se metabolizan bajo condiciones fisiológicas o cuando se convierten por solvólisis, producen el compuesto activo deseado. Los profármacos incluyen, sin limitación, ésteres, amidas, carbamatos, carbonatos, ureidos, solvatos, o hidratos del compuesto activo. Típicamente, el profármaco es inactivo, o menos activo que el compuesto activo, pero puede proporcionar una o más propiedades favorables de manejo, administración, y/o metabólicas. Por ejemplo, algunos profármacos son ésteres del compuesto activo; durante la metabólisis, el grupo éster se escinde para producir el fármaco activo. Los ésteres incluyen, por ejemplo, ésteres de un grupo de ácido carboxílico, o derivados S-acilo u O-acilo de grupos tiol, alcohol, o fenol. En este contexto, un ejemplo común es un alquil éster de un ácido carboxílico. Los profármacos también pueden incluir variantes en donde un grupo -NH del compuesto se ha sometido a acilación, tal como la posición 7 del anillo pirrolo[2,3-d]pirimidina, la posición 1 del anillo 1H-pirrolo[2,3-b]piridina, o el nitrógeno del grupo sulfonamida de los compuestos, como se describe en este documento, donde la escisión del grupo acilo proporciona el grupo libre -NH del fármaco activo. Algunos profármacos se activan enzimáticamente para producir el compuesto activo, o un compuesto puede someterse a una reacción química posterior para producir el compuesto activo. Los profármacos pueden proceder de la forma profármaco a la forma activa en una sola etapa, o pueden tener una o más formas intermedias que pueden tener actividad por sí mismas o pueden ser inactivas.

[0179] Como se describe en *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, CA, 2001), los profármacos pueden dividirse conceptualmente en dos categorías no exclusivas, profármacos bioprecursores y profármacos portadores. Generalmente, los profármacos bioprecursores son compuestos que son inactivos o tienen baja actividad en comparación con el compuesto farmacológico activo correspondiente, que contienen uno o más grupos protectores y se convierten a una forma activa por el metabolismo o solvólisis. Tanto la forma farmacológica activa como cualquier producto metabólico liberado, deben tener una toxicidad aceptablemente baja. Típicamente, la formación del compuesto farmacológico activo implica un proceso o reacción metabólica que es de uno de los siguientes tipos:

[0180] Reacciones oxidativas: Las reacciones oxidativas se ejemplifican sin limitación por reacciones tales como oxidación de las funcionalidades alcohol, carbonilo, y ácido, hidroxilación de carbonos alifáticos, hidroxilación de átomos de carbono alicíclicos, oxidación de átomos de carbono aromáticos, oxidación de dobles enlaces carbono-carbono, oxidación de grupos funcionales que contienen nitrógeno, oxidación de silicio, fósforo, arsénico y azufre, N-desalquilación oxidativa, O- y S-desalquilación oxidativa, desaminación oxidativa, así como otras reacciones oxidativas.

[0181] Reacciones reductoras: Las reacciones reductoras se ejemplifican sin limitación por reacciones tales como la reducción de funcionalidades carbonilo, reducción de funcionalidades alcohol y dobles enlaces carbono-carbono, reducción de grupos funcionales que contienen nitrógeno, y otras reacciones de reducción.

[0182] Reacciones sin cambio en el estado de oxidación: Las reacciones sin cambio en el estado de oxidación se ejemplifican sin limitación por reacciones tales como hidrólisis de ésteres y éteres, escisión hidrolítica de enlaces sencillos carbono-nitrógeno, escisión hidrolítica de heterociclos no aromáticos, hidratación y deshidratación en múltiples enlaces, nuevos enlaces atómicos que resultan de reacciones de deshidratación, deshalogenación hidrolítica, remoción de moléculas de haluro de hidrógeno, y otras reacciones semejantes.

[0183] Los profármacos portadores son compuestos farmacológicos que contienen una porción de transporte, por ejemplo, que mejora la asimilación y/o el suministro localizado a un sitio o sitios de acción. De manera deseable para tal profármaco portador, el enlace entre la porción farmacológica y la porción de transporte es un enlace covalente, el profármaco es inactivo o menos activo que el compuesto farmacológico, el profármaco y cualquier porción de transporte de liberación son aceptablemente no tóxicos. Para los profármacos donde la porción de transporte pretende aumentar la asimilación, típicamente la liberación de la porción de transporte debe ser rápida. En otros casos, es deseable utilizar una porción que proporciona una liberación lenta, por ejemplo, ciertos polímeros u otras porciones, tales como ciclodextrinas. (Véase, por ejemplo, Cheng et al., Publ. de Patente de E.U. No. 20040077595, Solic. No. 10/656,838, incorporada en este documento para referencia). Tales profármacos portadores a menudo son favorables para los fármacos administrados en forma oral. En algunos casos, la porción de transporte proporciona un suministro orientado del fármaco, por ejemplo el fármaco puede conjugarse a un anticuerpo o fragmento de anticuerpo. Los profármacos portadores pueden, por ejemplo, utilizarse para mejorar una o más de las siguientes propiedades: lipofilicidad incrementada, duración incrementada de los efectos farmacológicos, especificidad de sitio incrementada, toxicidad y reacciones adversas reducidas, y/o mejora en la formulación farmacológica (por ejemplo, estabilidad, solubilidad en agua, depresión de una propiedad organoléptica o fisioquímica indeseable). Por ejemplo, la lipofilicidad puede incrementarse por la esterificación de grupos hidroxilo con ácidos carboxílicos lipofílicos, o de grupos de ácido carboxílico con alcoholes, por ejemplo, alcoholes alifáticos. Wermuth, *supra*.

[0184] Los metabolitos, por ejemplo, metabolitos activos, se superponen con los profármacos, como se describe anteriormente, por ejemplo, profármacos bioprecursores. De esta manera, tales metabolitos son compuestos farmacológicamente activos o compuestos que se metabolizan además a compuestos

farmacológicamente activos que son derivados resultantes de procesos metabólicos en el cuerpo de un sujeto. De estos, los metabolitos activos son tales compuestos derivados farmacológicamente activos. Para los profármacos, el compuesto profarmacológico generalmente es inactivo o de actividad inferior a la del producto metabólico. Para los metabolitos activos, el compuesto original puede ser un compuesto activo o puede ser un profármaco inactivo. Por ejemplo, en algunos compuestos, uno o más grupos alcoxi pueden metabolizarse a grupos hidroxilo mientras se retiene la actividad farmacológica, y/o pueden esterificarse grupos carboxilo, por ejemplo, la glucuronidación. En algunos casos, puede haber más de un metabolito, donde un metabolito o metabolitos intermediarios se metaboliza además para proporcionar un metabolito activo. Por ejemplo, en algunos casos, un compuesto derivado que resulta de la glucuronidación metabólica puede ser inactivo o de baja actividad, y puede metabolizarse posteriormente para proporcionar un metabolito activo.

[0185] Los metabolitos de un compuesto pueden identificarse utilizando técnicas de rutina conocidas en la materia, y sus actividades pueden determinarse al utilizar pruebas tales como las descritas en este documento. Véase, por ejemplo, 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

[0186] Se entiende que algunos compuestos pueden exhibir tautomerismo. En tales casos, las fórmulas proporcionadas en este documento representan expresamente sólo una de las formas tautoméricas posibles. Por lo tanto, debe entenderse que las fórmulas proporcionadas en este documento pretenden representar cualquier forma tautomérica de los compuestos representados y no deben limitarse meramente a la forma tautomérica específica representada por los dibujos de las fórmulas.

[0187] Asimismo, algunos de los compuestos de acuerdo con la presente invención pueden existir como estereoisómeros, es decir, que tienen la misma conectividad atómica de los átomos enlazados de manera covalente, y que difieren aún en la orientación espacial de los átomos. Por ejemplo, los compuestos pueden ser estereoisómeros ópticos, que contienen uno o más centros quirales y, por lo tanto, pueden existir en dos o más formas estereoisoméricas (por ejemplo, enantiómeros o diastereómeros). De esta manera, tales compuestos pueden presentarse como estereoisómeros únicos (es decir, esencialmente libres de otros estereoisómeros), racematos, y/o mezclas de enantiómeros y/o diastereómeros. Como otro ejemplo, los estereoisómeros incluyen isómeros geométricos, tal como la orientación *cis-* o *trans-* de los sustituyentes en carbonos adyacentes de un doble enlace. Todos los estereoisómeros únicos semejantes, racematos, y mezclas de los mismos, pretenden estar dentro del alcance de la presente invención. A menos que se especifique lo contrario, todas las formas estereoisoméricas semejantes se incluyen dentro de las fórmulas proporcionadas en este documento.

[0188] En algunas modalidades, un compuesto quiral de la presente invención está en una forma que contiene por lo menos 80% de un solo isómero (60% de exceso enantiomérico ("e.e.") o exceso diastereomérico ("d.e.")), o por lo menos 85% (70% de e.e. o d.e.), 90% (80% de e.e. o d.e.), 95% (90% de e.e. o d.e.), 97.5% (95% de e.e. o d.e.), o 99% (98% de e.e. o d.e.). Como se entiende generalmente por los expertos en la técnica, un compuesto ópticamente puro que tiene un centro quiral es uno que consiste

esencialmente en uno de los dos posibles enantiómeros (es decir, es enantioméricamente puro), y un compuesto ópticamente puro que tiene más de un centro quiral es uno que es tanto diastereoméricamente puro como enantioméricamente puro. En algunas modalidades, el compuesto se presenta en forma ópticamente pura, y tal forma ópticamente pura se prepara y/o aísla por métodos conocidos en la técnica (por ejemplo, por técnicas de recristalización, técnicas de síntesis quiral (incluyendo síntesis a partir de materiales de inicio ópticamente puros), y separación cromatográfica utilizando una columna quiral.

(c) Sales farmacéuticamente aceptables

[0189] A menos que se especifique lo contrario, la especificación de un compuesto en este documento incluye sales farmacéuticamente aceptables de tal compuesto. De esta manera, los compuestos descritos en este documento pueden estar en forma de sales farmacéuticamente aceptables, o pueden formularse como sales farmacéuticamente aceptables. Las formas de sal farmacéuticamente aceptable contempladas incluyen, sin limitación, mono, bis, tris, tetrakis, etcétera. Las sales farmacéuticamente aceptables no son tóxicas en las cantidades y concentraciones a las cuales se administran. La preparación de tales sales puede facilitar el uso farmacológico al alterar las características físicas de un compuesto sin evitar que ejerza su efecto fisiológico. Las alteraciones útiles en las propiedades físicas incluyen reducir el punto de fusión para facilitar la administración a través de mucosas e incrementar la solubilidad para facilitar la administración de concentraciones superiores del fármaco. Un compuesto de la invención puede poseer un grupo suficientemente ácido, uno suficientemente básico, o ambos grupos funcionales y, por consiguiente, puede reaccionar con cualquiera de una serie de bases inorgánicas u orgánicas, y ácidos inorgánicos y orgánicos, para formar una sal farmacéuticamente aceptable.

[0190] Sales farmacéuticamente aceptables incluyen sales de adición de ácido tales como aquellas que contienen cloruro, bromuro, yoduro, clorhidrato, acetato, fenilacetato, acrilato, ascorbato, aspartato, benzoato, 2-fenoxibenzoato, 2-acetoxibenzoato, dinitrobenzoato, hidroxibenzoato, metoxibenzoato, metilbenzoato, bicarbonato, butino-1,4 dioato, hexino-1,6-dioato, caproato, caprilato, clorobenzoato, cinamato, citrato, decanoato, formato, fumarato, glicolato, gluconato, glucarato, glucuronato, glucosa-6-fosfato, glutamato, heptanoato, hexanoato, isetionato, isobutirato, gamma-hidroxibutirato, fenilbutirato, lactato, malato, maleato, hidroximaleato, metilmaleato, malonato, mandelato, nicotinato, nitrato, isonicotinato, octanoato, oleato, oxalato, pamoato, fosfato, monofosfato ácido, difosfato ácido, ortofosfato, metafosfato, pirofosfato, 2-fosfoglicerato, 3-fosfoglicerato, ftalato, propionato, fenilpropionato, propiolato, piruvato, quinato, salicilato, 4-aminosalicilato, sebacato, estearato, suberato, succinato, sulfato, pirosulfato, bisulfato, sulfito, bisulfito, sulfamato, sulfonato, bencensulfonato (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*-toluensulfonato (es decir, tosilato), xilensulfonatos, ciclohexilsulfamato, tartrato, y trifluoroacetato. Estas sales de adición de ácido farmacéuticamente aceptables pueden prepararse al utilizar el ácido correspondiente apropiado.

[0191] Cuando se presentan grupos funcionales ácido, tal como ácido carboxílico o fenol, las sales farmacéuticamente aceptables también incluyen sales de adición de base tales como las que contienen

benzatina, cloroprocaína, colina, etanolamina, dietanolamina, trietanolamina, t-butilamina, diciclohexilamina, etilendiamina, N,N'-dibenciletilendiamina, meglumina, hidroxietilpirrolidina, piperidina, morfolina, piperazina, procaína, aluminio, calcio, cobre, hierro, litio, magnesio, manganeso, potasio, sodio, zinc, amonio, y mono-, di-, o tri-alquilaminas (por ejemplo, dietilamina), o sales derivadas de aminoácidos tales como 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 farmacéuticamente aceptables pueden prepararse al utilizar la base correspondiente apropiada.

[0192] Las sales farmacéuticamente aceptables pueden prepararse por técnicas estándar. Por ejemplo, la forma de base libre de un compuesto puede disolverse en un solvente adecuado, tal como una solución acuosa o acuosa-alcohólica que contiene el ácido apropiado, y luego aislarse al evaporar la solución. En otro ejemplo, una sal puede prepararse al hacer reaccionar la base y ácido libres en un solvente orgánico. Si el compuesto particular es un ácido, la sal farmacéuticamente aceptable deseada puede prepararse por cualquier método adecuado, por ejemplo, el tratamiento del ácido libre con una base inorgánica u orgánica apropiada.

(d) Otras formas de compuestos

[0193] En el caso de los agentes que son sólidos, se entiende por los expertos en la técnica que los compuestos y sales pueden existir en diferentes formas cristalinas o polimórficas, o pueden formularse como co-cristales, o pueden estar en forma amorfa, o pueden ser cualquier combinación de las mismas (por ejemplo, parcialmente cristalina, parcialmente amorfa, o mezclas de polimorfos) todas las cuales pretenden estar dentro del alcance de la presente invención y fórmulas especificadas. Aunque las sales se forman por adición de ácido/base, es decir, una base libre o ácido libre del compuesto de interés forma una reacción ácido/base con una correspondiente base de adición o ácido de adición, respectivamente, lo que resulta en una interacción de cargas iónicas, los co-cristales son una nueva especie química que se forma entre compuestos neutros, lo que resulta en el compuesto y una especie molecular adicional en la misma estructura cristalina.

[0194] En algunos casos, los compuestos de la invención forman complejos con un ácido o una base, incluyendo sales de adición de base tales como amonio, dietilamina, etanolamina, etilendiamina, dietanolamina, t-butilamina, piperazina, meglumina; sales de adición de ácido, tales como acetato, acetilsalicilato, besilato, camsilato, citrato, formato, fumarato, glutarato, clorhidrato, maleato, mesilato, nitrato, oxalato, fosfato, succinato, sulfato, tartrato, tiocianato y tosilato; y aminoácidos tales como alanina, arginina, asparagina, ácido aspártico, cisteína, glutamina, ácido glutámico, glicina, histidina, isoleucina, leucina, lisina, metionina, fenilalanina, prolina, serina, treonina, triptofano, tirosina o valina. Al combinar el compuesto de la invención con el ácido o base, se forma preferiblemente un complejo amorfo en lugar de un material cristalino, tal como una sal típica o co-cristal. En algunos casos, la forma amorfa del complejo se facilita por un procesamiento adicional, tal como por secado por aspersión, métodos mecanoquímicos tal como compactación por rodillos, o irradiación de microondas del compuesto original mezclado con el ácido o base. Tales métodos también pueden incluir la adición de

sistemas poliméricos iónicos y/o no iónicos, incluyendo, pero sin limitarse a, acetato succinato de hidroxipropil metil celulosa (HPMCAS) y copolímero de ácido metacrílico (por ejemplo, Eudragit® L100-55), que estabilizan además la naturaleza amorfa del complejo. Tales complejos amorfos proporcionan varias ventajas. Por ejemplo, la disminución de la temperatura de fusión en relación con la base libre facilita el procesamiento adicional, tal como la extrusión de fundido en caliente, para mejorar además las propiedades biofarmacéuticas del compuesto. También, el complejo amorfo es fácilmente friable, lo que proporciona una compresión mejorada para la carga del sólido a una forma de cápsula o tableta.

[0195] Adicionalmente, las fórmulas pretenden cubrir formas hidratadas o solvatadas, así como no hidratadas o no solvatadas de las estructuras identificadas. Por ejemplo, los compuestos indicados incluyen formas tanto hidratadas como no hidratadas. Otros ejemplos de solvatos incluyen las estructuras en combinación con un solvente adecuado, tal como isopropanol, etanol, metanol, dimetil sulfóxido, etil acetato, ácido acético, o etanolamina.

Formulaciones y administración

[0196] Los métodos y compuestos típicamente se utilizarán en la terapia para sujetos humanos. Sin embargo, también pueden utilizarse para tratar indicaciones similares o idénticas en otros sujetos animales. Los compuestos descritos en este documento pueden administrarse por diferentes rutas, incluyendo inyección (es decir, parenteral, incluyendo intravenosa, intraperitoneal, subcutánea, e intramuscular), oral, transdérmica, a través de mucosas, rectal, o inhalante. Tales formas de dosificación deben permitir que el compuesto alcance las células objetivo. Otros factores se conocen bien en la técnica, e incluyen consideraciones tales como la toxicidad y formas de dosificación que retardan al compuesto o composición para que ejerza sus efectos. Técnicas y formulaciones generalmente pueden encontrarse en Remington: *The Science and Practice of Pharmacy*, 21ª edición, Lippincott, Williams and Wilkins, Philadelphia, PA, 2005 (incorporada por la presente para referencia en este documento).

[0197] En algunas modalidades, las composiciones comprenderán portadores o excipientes farmacéuticamente aceptables, tales como rellenos, aglutinantes, desintegrantes, agentes de flujo, lubricantes, agentes de complejo, solubilizantes, y tensoactivos, los cuales pueden elegirse para facilitar la administración del compuesto por una ruta particular. Ejemplos de portadores incluyen carbonato de calcio, fosfato de calcio, diversos azúcares tales como lactosa, glucosa, o sacarosa, tipos de almidón, derivados de celulosa, gelatina, lípidos, liposomas, nanopartículas, y similares. Los portadores también incluyen líquidos fisiológicamente compatibles 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, polietilenglicoles, parafina líquida, y similares. Los excipientes también pueden incluir, por ejemplo, dióxido de silicio coloidal, gel de sílice, talco, silicato de magnesio, silicato de calcio, aluminosilicato de sodio, trisilicato de magnesio, celulosa pulverizada, celulosa macrocristalina, carboximetilcelulosa, carboximetilcelulosa sódica reticulada, benzoato de sodio, carbonato de calcio, carbonato de magnesio, ácido esteárico, estearato de aluminio, estearato de calcio, estearato de magnesio, estearato de zinc,

estearilfumarato de sodio, siloide, estearowet C, óxido de magnesio, almidón, glicolato de almidón sódico, monoestearato de glicerilo, dibehenato de glicerilo, palmitoestearato de glicerilo, aceite vegetal hidrogenado, aceite hidrogenado de semilla de algodón, aceite mineral de aceite de semillas de ricino, polietilenglicol (por ejemplo, PEG 4000-8000), polioxietilenglicol, poloxámeros, povidona, crospovidona, croscarmelosa sódica, ácido algínico, caseína, copolímero ácido metacrílico divinilbenceno, docusato de sodio, ciclodextrinas (por ejemplo, 2-hidroxipropil-.delta.-ciclodextrina), polisorbatos (por ejemplo, polisorbato 80), cetrimida, TPGS (d-alfa-tocoferilo polietilenglicol 1000 succinato), laurilsulfato de magnesio, laurilsulfato de sodio, polietilenglicoléteres, di-éster de ácidos grasos de polietilenglicoles, o un éster de polioxialquilensorbitan de ácidos grasos (por ejemplo, polioxietilensorbitanéster Tween®), polioxietilensorbitanésteres de ácidos grasos, sorbitanéster de ácidos grasos, por ejemplo, un sorbitanéster de ácidos grasos de un ácido graso tal como ácido oleico, esteárico o palmítico, manitol, xilitol, sorbitol, maltosa, lactosa, lactosa monohidratada o lactosa seca 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, polidextrosam, quitosana, gelatina, HPMC (hidroxipropilmetilcelulosas), HPC (hidroxipropilcelulosa), hidroxietilcelulosa, y similares.

[0198] En algunas modalidades, puede utilizarse la administración oral. Las preparaciones farmacéuticas para su uso oral pueden formularse en formas convencionales de dosificación oral, tales como cápsulas, tabletas, y preparaciones líquidas tales como jarabes, elíxires, y gotas concentradas. Los compuestos descritos en este documento pueden combinarse con excipientes sólidos, moliendo opcionalmente una mezcla resultante, y procesando la mezcla de gránulos, después de agregar auxiliares adecuados, si se desea, para obtener, por ejemplo, tabletas, tabletas recubiertas, cápsulas duras, cápsulas suaves, soluciones (por ejemplo, soluciones acuosas, alcohólicas, u oleosas) y similares. Los excipientes adecuados son, en particular, rellenos tales como 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 tragacanto, metilcelulosa, hidroxipropilmetil-celulosa, carboximetilcelulosa sódica (CMC), y/o polivinilpirrolidona (PVP: povidona); excipientes oleosos, incluyendo aceites vegetales y animales, tales como aceite de girasol, aceite de oliva, o aceite de hígado de bacalao. Las formulaciones de dosificación oral también pueden contener agentes desintegrantes, tal como la polivinilpirrolidona reticulada, agar, o ácido algínico, o una sal de los mismos, tal como alginato de sodio; un lubricante, tal como talco o estearato de magnesio; un plastificante, tal como glicerol o sorbitol; un edulcorante tal como sacarosa, fructosa, lactosa, o aspartame; un agente saborizante natural o artificial, tal como menta piperina, aceite de hierbabuena, o saborizante de cereza; o colorantes o pigmentos, que pueden utilizarse para la identificación o caracterización de diferentes dosis o combinaciones. También se proporcionan centros de grageas con recubrimientos adecuados. Para este propósito, pueden utilizarse soluciones concentradas de azúcar, que pueden contener opcionalmente, por ejemplo, goma arábiga, talco, poli-vinilpirrolidona, gel carbopol, polietilenglicol, y/o dióxido de titanio, soluciones de laca, y solventes o mezclas de solventes orgánicos adecuados.

[0199] Las preparaciones farmacéuticas que pueden utilizarse en forma oral incluyen cápsulas rígidas hechas de gelatina ("gelcaps"), así como cápsulas suaves selladas hechas de gelatina, y un plastificante,

tal como glicerol o sorbitol. Las cápsulas rígidas pueden contener los ingredientes activos en mezcla con un relleno tal como lactosa, aglutinantes tales como almidones, y/o lubricantes tales como talco o estearato de magnesio y, opcionalmente, estabilizantes. En las cápsulas suaves, los compuestos activos pueden disolverse o suspenderse en líquidos adecuados, tales como aceites grasos, parafina líquida, o polietilenglicoles líquidos.

[0200] En algunas modalidades, puede utilizarse inyección (administración parenteral), por ejemplo, intramuscular, intravenosa, intraperitoneal, y/o subcutánea. Los compuestos descritos en este documento para inyección pueden formularse en soluciones líquidas estériles, preferiblemente en reguladores o soluciones fisiológicamente compatibles, tales como solución salina, solución de Hank, o solución de Ringer. También pueden prepararse dispersiones en soluciones no acuosas, tales como glicerol, propilenglicol, etanol, polietilenglicoles líquidos, triacetina, y aceites vegetales. Las soluciones también pueden contener un conservador, tal como metilparabeno, propilparabeno, clorobutanol, fenol, ácido sórbico, timerosal, y similares. Además, los compuestos pueden formularse en forma sólida, incluyendo, por ejemplo, formas liofilizadas, y redisolverse o suspenderse antes de su uso.

[0201] En algunas modalidades, puede usarse administración a través de mucosas, tópica o transdérmica. En tales formulaciones de los compuestos descritos en este documento, se usan penetrantes apropiados para la barrera que se traspasará. Tales penetrantes generalmente se conocen en la técnica, e incluyen, por ejemplo, para la administración a través de mucosas, sales biliares y derivados de ácido fusídico. Además, pueden utilizarse detergentes para facilitar la penetración. La administración a través de mucosas, por ejemplo, puede ser a través de aspersiones nasales o supositorios (rectales o vaginales). Las composiciones de los compuestos descritos en este documento para administración tópica pueden formularse como aceites, cremas, lociones, ungüentos, y similares por la elección de portadores apropiados conocidos en la técnica. Los portadores adecuados incluyen aceites vegetales o minerales, vaselina (parafina blanca suave), grasas o aceites de cadena ramificada, grasas animales y alcohol de alto peso molecular (más de C_{12}). En algunas modalidades, los portadores se seleccionan de tal modo que el ingrediente activo sea soluble. Emulsionantes, estabilizantes, humectantes y antioxidantes también pueden incluirse, así como agentes que imparten color o fragancia, si se desea. Las cremas para aplicación tópica se formulan preferiblemente a partir de una mezcla de aceite mineral, cera de abejas de auto emulsión y agua, en cuya mezcla el ingrediente activo, disuelto en una pequeña cantidad de solvente (por ejemplo, un aceite), se mezcla. Adicionalmente, la administración por medios transdérmicos puede comprender un parche o apósito transdérmico, tal como un vendaje impregnado con un ingrediente activo y, opcionalmente, uno o más portadores o diluyentes conocidos en la técnica. Para administrarse en forma de un sistema de suministro transdérmico, la administración de la dosificación será continua, en lugar de intermitente, a lo largo del régimen de dosificación.

[0202] En algunas modalidades, los compuestos se administran como inhalantes. 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 en la técnica. Por ejemplo, los polvos pueden incluir una base de polvo adecuada, tal como lactosa o almidón, y las soluciones pueden comprender propilenglicol, agua estéril, etanol, cloruro de sodio y otros aditivos, tales

como sales de ácido, álcali y reguladoras. Tales soluciones o suspensiones pueden administrarse al inhalar mediante aspersión, bomba, atomizador, o nebulizador, y similares. Los compuestos descritos en este documento también pueden usarse en combinación con otras terapias inhaladas, por ejemplo corticosteroides tales como propionato de fluticasona, dipropionato de beclometasona, triamcinolona acetonida, budesonida, y furoato de mometasona; beta agonistas tales como albuterol, salmeterol, y formoterol; agentes anticolinérgicos tales como bromuro de ipratroprio o tiotropio; vasodilatadores tales como treprostinal e iloprost; enzimas tales como DNAasa; proteínas terapéuticas; anticuerpos de inmunoglobulina; un oligonucleótido, tal como DNA o RNA de una sola o doble hebra, siRNA; antibióticos tales como tobramicina; antagonistas de receptores muscarínicos; antagonistas de leucotrienos; antagonistas de citocinas; inhibidores de proteasas; cromolin sódico; nedocril sódico; y cromoglicato de sodio.

[0203] Las cantidades de los diversos compuestos que se administraran pueden determinarse por procedimientos estándar tomando en cuenta factores tales como la actividad del compuesto (*in vitro*, por ejemplo, la IC_{50} del compuesto vs. objetivo, o la actividad *in vivo* en modelos animales de eficacia), resultados de farmacocinética en modelos animales (por ejemplo, vida media biológica o biodisponibilidad), la edad, tamaño, y peso del sujeto, y el trastorno asociado con el sujeto. La importancia de estos y otros factores se conoce bien por los expertos en la técnica. Generalmente, una dosis estará en el intervalo de alrededor de 0.01 a 50 mg/kg, también alrededor de 0.1 a 20 mg/kg del sujeto que se trata. Pueden utilizarse múltiples dosis.

[0204] Los compuestos descritos en este documento también pueden utilizarse en combinación con otras terapias para tratar la misma enfermedad. Tal uso de combinaciones incluye la administración de los compuestos y uno o más terapéuticos diferentes en momentos diferentes, o la co-administración del compuesto y una o más terapias diferentes. En algunas modalidades, la dosificación puede modificarse para uno o más de los compuestos de la invención u otros terapéuticos utilizados en combinación, por ejemplo, la reducción en la cantidad dosificada en relación con un compuesto o terapia utilizada sola, por métodos bien conocidos por los expertos en la técnica.

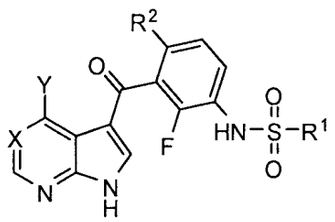
[0205] Se entenderá que el uso en combinación incluye el uso con otras terapias, fármacos, procedimientos médicos, etc., en donde la otra terapia o procedimiento puede administrarse en períodos diferentes (por ejemplo, dentro de un tiempo corto, tal como en el lapso de horas (por ejemplo, 1, 2, 3, 4-24 horas), o dentro de un tiempo prolongado (por ejemplo, 1-2 días, 2-4 días, 4-7 días, 1-4 semanas)) a los de un compuesto descrito en este documento, o al mismo tiempo que un compuesto descrito en este documento. El uso en combinación también incluye el uso con una terapia o procedimiento médico que se administra una vez u ocasionalmente, tal como cirugía, junto con un compuesto descrito en este documento administrado dentro de un período corto o período prolongado, antes o después de la otra terapia o procedimiento. En algunas modalidades, la presente invención permite el suministro de un compuesto descrito en este documento y uno o más terapéuticos farmacológicos diferentes suministrados por una ruta diferente de administración o por la misma ruta de administración. El uso en combinación para cualquier ruta de administración incluye el suministro de un compuesto descrito en este documento y uno o más terapéuticos farmacológicos diferentes suministrados por la misma ruta de administración en

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conjunto en cualquier formulación, incluyendo formulaciones donde los dos compuestos se enlazan químicamente en tal forma que mantienen su actividad terapéutica cuando se administraron. En un aspecto, la otra terapia farmacológica puede co-administrarse con un compuesto descrito en este documento. El uso en combinación por la co-administración incluye la administración de co-formulaciones o formulaciones de compuestos unidos químicamente, o la administración de dos o más compuestos en formulaciones separadas dentro de un período corto de tiempo entre sí (por ejemplo, en el lapso de una hora, 2 horas, 3 horas, hasta 24 horas), administradas por la misma o diferentes rutas. La co-administración de formulaciones separadas incluye la co-administración por el suministro mediante un dispositivo, por ejemplo, el mismo dispositivo inhalante, la misma jeringa, etc., o la administración desde dispositivos separados dentro de un intervalo corto entre sí. Las co-formulaciones de un compuesto descrito en este documento y una o más farmacoterapias adicionales suministradas por la misma ruta incluyen preparación de los materiales en conjunto de tal modo que puedan administrarse por un dispositivo, incluyendo los compuestos separados combinados en una formulación, o compuestos que se modifican de tal modo que se asocian químicamente, y todavía mantienen aún su actividad biológica. Tales compuestos químicamente asociados pueden tener un enlace que se mantiene sustancialmente *in vivo*, o el enlace puede romperse *in vivo*, lo que separa los dos componentes activos.

[0206] Además de las descripciones en este documento, las siguientes modalidades no limitantes se contemplan en este documento:

1. Un compuesto que tiene la estructura química de la Fórmula I,



Fórmula I

o una sal, hidrato o solvato farmacéuticamente aceptable del mismo,

en donde:

X es –N= o –C(R^5)=;

Y se selecciona del grupo que consiste en flúor, cloro, bromo, yodo, alquilo inferior, alcoxi inferior, haloalquilo, CN, -OH, cicloalquilo, -OR^8, y –N(R^3)(R^4); en donde:

R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en (i) hidrógeno, -OR^8 y alquilo inferior opcionalmente sustituido con uno o más R^{11}; (ii) cicloalquilo o cicloalquilalquilo, cada uno de los cuales se sustituye opcionalmente con uno o más R^{12}; (iii) heterocicloalquilo o heterocicloalquilalquilo, cada uno de los cuales se sustituye opcionalmente con uno o más R^{13}; (iv) arilo o arilalquilo, cada uno de los cuales se sustituye opcionalmente con uno o más R^{14}, opcionalmente, en donde los dos grupos R^{14} adyacente en el anillo arilo se toman en conjunto para formar un anillo aromático hetero cíclico de 5 o 6 miembros que tiene de 1-4 heteroátomos seleccionados de O o N; y (v) heteroarilo o heteroarilalquilo, cada uno de los cuales se sustituye opcionalmente con uno o más R^{15}; o

R^3 y R^4 son alquilo inferior; o

R^3 y R^4 se combinan con el átomo de nitrógeno al cual se unen para formar un anillo de 3-7 miembros que tiene 0-1 heteroátomo de anillo adicional seleccionado de O, N o S, en donde el átomo de nitrógeno o azufre se oxida opcionalmente;

R^1 se selecciona del grupo que consiste en alquilo inferior, haloalquilo, haloalcoxi, alquilo inferior sustituido con flúor, cicloalquilo opcionalmente sustituido con uno o más R^7, heterocicloalquilo, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, arilo opcionalmente sustituido con uno o más R^6 y heteroarilo opcionalmente sustituido con uno o más R^7;

R^2 es hidrógeno, flúor, cloro o alquilo inferior opcionalmente sustituido con uno o más flúor;

R^5 se selecciona del grupo que consiste en hidrógeno, flúor, cloro, -CN, alquilo inferior opcionalmente sustituido con uno o más R^{16}, y alcoxi inferior opcionalmente sustituido con uno o más R^{17};

cada R^6, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, cloro, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, -C(O)-O-R^{15}, -N(H)-C(O)-R^{16}, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior; o dos R^5 en carbonos adyacentes se combinan para formar un heterocicloalquilo fusionado opcionalmente sustituido con uno o más alquilo inferior;

cada R^7, cuando se presenta, se selecciona independientemente del grupo que consiste en alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, -C(O)-O-R^{20}, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior;

R^8 es hidrógeno, alquilo inferior opcionalmente sustituido con uno o más flúor, o, cuando R^8 es un alquilo C_{2-6}, el alquilo opcionalmente puede sustituirse con uno o más R^{21}; cicloalquilo opcionalmente sustituido con uno o más R^{21}, o heterocicloalquilo opcionalmente sustituido con uno o más R^{21};

cada R^{11}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, cicloalquilo opcionalmente sustituido con uno o más R^{12}, heterocicloalquilo opcionalmente sustituido con uno o más R^{13}, arilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo opcionalmente sustituido con uno o más R^{15};

cada R^{12}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, -N(H)-C(O)-R^{22}, -N(H)-$S(O)_2$-R^{23}, C(O)-R^{24}, y $S(O)_2$-R^{25};

cada R^{13}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, -N(H)-C(O)-R^{26}, -N(H)-$S(O)_2$-R^{27}, C(O)-R^{28}, $S(O)_2$-R^{29}, y alquilo inferior opcionalmente sustituido con uno o más R^{30};

cada R^{14} y R^{15}, cuando se presenta, se seleccionan independientemente del grupo que consiste en flúor, cloro, -OH, $-NH_2$, -CN, $-NO_2$, -N(H)-C(O)-R^{31}, -N(H)-$S(O)_2$-R^{32}, C(O)-R^{33}, $S(O)_2$-R^{34}, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, arilo

opcionalmente sustituido con uno o más R^{35}, y heteroarilo opcionalmente sustituido con uno o más R^{36};

cada R^{16}, cuando se presenta, es independientemente flúor, -OH, alcoxi inferior, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{17}, cuando se presenta, es independientemente flúor, -OH, alcoxi inferior, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{18} y R^{20}, cuando se presentan, son independientemente hidrógeno, alquilo inferior, o alquilo inferior sustituido con flúor;

cada R^{19}, R^{22}, R^{23}, R^{26}, R^{27}, R^{31} y R^{32}, cuando se presentan, son independientemente alquilo inferior o alquilo inferior sustituido con flúor;

cada R^{21}, cuando se presenta, es flúor, -OH, alcoxi inferior, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{24}, R^{25}, R^{28}, R^{29}, R^{33}, y R^{34}, cuando se presentan, son independientemente alquilo inferior, alquilo inferior sustituido con flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{30}, cuando se presenta, es independientemente flúor, arilo opcionalmente sustituido con uno o más R^{35} o heteroarilo opcionalmente sustituido con uno o más R^{36}; y

cada R^{35} y R^{36}, cuando se presentan, se seleccionan independientemente del grupo que consiste en flúor, cloro, -OH, $-NH_2$, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino.

2. El compuesto de la modalidad 1, en donde:

X es -N= o $-C(R^5)=$; en donde R^5 se selecciona del grupo que consiste en hidrógeno, flúor, cloro, -CN, alquilo inferior y alcoxi inferior, en donde el alquilo inferior o alcoxi inferior se sustituye opcionalmente con de uno a tres grupos seleccionados de flúor, -OH, alcoxi inferior, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

Y se selecciona del grupo que consiste en flúor, cloro, bromo, yodo, alquilo inferior, alcoxi inferior, haloalquilo, CN, -OH, cicloalquilo, $-OR^8$, y $-N(R^3)(R^4)$; en donde:

R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en (i) hidrógeno, $-OR^8$ y alquilo inferior opcionalmente sustituido con de uno a tres R^{11}; (ii) cicloalquilo o cicloalquilalquilo, cada uno de los cuales se sustituye opcionalmente con de uno a tres R^{12}; (iii) heterocicloalquilo o heterocicloalquilalquilo, cada uno de los cuales se sustituye opcionalmente con de uno a tres R^{13}; (iv) arilo o arilalquilo, cada uno de los cuales se sustituye opcionalmente con de uno a tres R^{14} opcionalmente, en donde los dos grupos R^{14} adyacentes en el anillo arilo se toman en conjunto para formar un anillo aromático heterocíclico de 5 o 6 miembros que tiene de 1-4 heteroátomos seleccionados de O o N; y (v) heteroarilo o heteroarilalquilo, cada uno de los cuales se sustituye opcionalmente con de uno a tres R^{15}; o

R^3 y R^4 son alquilo inferior; o

R^3 y R^4 se combinan con el átomo de nitrógeno al cual se unen para formar un anillo de tres a siete miembros que tiene 0-1 heteroátomo de anillo adicional seleccionado de O, N o S, en donde el átomo de nitrógeno o azufre se oxida opcionalmente;

R^1 se selecciona del grupo que consiste en alquilo inferior, haloalquilo, haloalcoxi, alquilo inferior sustituido con flúor, cicloalquilo opcionalmente sustituido con uno a tres R^7, heterocicloalquilo, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, arilo opcionalmente sustituido con uno a tres R^6 y heteroarilo opcionalmente sustituido con uno a tres R^7;

R^2 es hidrógeno, flúor, cloro, o alquilo inferior opcionalmente sustituido con de uno a cinco átomos de flúor;

cada R^6, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, cloro, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, $-C(O)-O-R^{15}$, $-N(H)-C(O)-R^{16}$, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior; o dos R^5 en carbonos adyacentes se combinan para formar un heterocicloalquilo fusionado opcionalmente sustituido con uno o más alquilo inferior;

cada R^7, cuando se presenta, se selecciona independientemente del grupo que consiste en alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, $-C(O)-O-R^{20}$, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior;

R^8 es hidrógeno, alquilo inferior opcionalmente sustituido con uno o más flúor, o, cuando R^8 es un alquilo C_{2-6}, el alquilo opcionalmente puede sustituirse con uno o más R^{21}; cicloalquilo opcionalmente sustituido con uno o más R^{21}, o heterocicloalquilo opcionalmente sustituido con uno o más R^{21};

cada R^{11}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, cicloalquilo opcionalmente sustituido con uno o más R^{12}, heterocicloalquilo opcionalmente sustituido con uno o más R^{13}, arilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo opcionalmente sustituido con uno o más R^{15};

cada R^{12}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, $-N(H)-C(O)-R^{22}$, $-N(H)-S(O)_2-R^{23}$, $C(O)-R^{24}$, y $S(O)_2-R^{25}$;

cada R^{13}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, $-N(H)-C(O)-R^{26}$, $-N(H)-S(O)_2-R^{27}$, $C(O)-R^{28}$, $S(O)_2-R^{29}$, y alquilo inferior opcionalmente sustituido con uno o más R^{30};

cada R^{14} y R^{15}, cuando se presenta, se seleccionan independientemente del grupo que consiste en flúor, cloro, -OH, $-NH_2$, -CN, $-NO_2$, $-N(H)-C(O)-R^{31}$, $-N(H)-S(O)_2-R^{32}$, $C(O)-R^{33}$, $S(O)_2-R^{34}$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, arilo opcionalmente sustituido con uno a tres R^{35}, y heteroarilo opcionalmente sustituido con uno a tres R^{36};

cada R^{18} y R^{20}, cuando se presentan, son independientemente hidrógeno, alquilo inferior, o alquilo inferior sustituido con flúor;

cada R^{19}, R^{22}, R^{23}, R^{26}, R^{27}, R^{31} y R^{32}, cuando se presentan, son independientemente alquilo inferior o alquilo inferior sustituido con flúor;

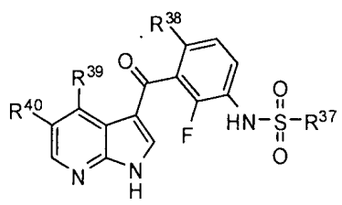
cada R^{21}, cuando se presenta, es flúor, -OH, alcoxi inferior, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{24}, R^{25}, R^{28}, R^{29}, R^{33}, y R^{34}, cuando se presentan, son independientemente alquilo inferior, alquilo inferior sustituido con flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{30}, cuando se presenta, es independientemente flúor, arilo opcionalmente sustituido con uno o más R^{35} o heteroarilo opcionalmente sustituido con uno a tres R^{36}; y

cada R^{35} y R^{36}, cuando se presentan, se seleccionan independientemente del grupo que consiste en flúor, cloro, -OH, $-NH_2$, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino.

3. El compuesto de la modalidad 1 o 2, que tiene la Fórmula II:



II

en donde:

R^{37} se selecciona del grupo que consiste en alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilo, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, fenilo opcionalmente sustituido con uno o más R^{41} y heteroarilo opcionalmente sustituido con uno o más R^{42};

R^{38} es hidrógeno, flúor, cloro o alquilo inferior opcionalmente sustituido con uno o más flúor;

R^{39} y R^{40} se seleccionan cada uno independientemente del grupo que consiste en flúor, cloro, -CN, -OH, $-NH_2$, alcoxi inferior, alquilo inferior opcionalmente sustituido con uno o más R^{43}, alquenilo inferior opcionalmente sustituido con C(O)-O-R^{44}, alquinilo inferior opcionalmente sustituido con alquilo inferior opcionalmente sustituido con uno o más flúor, o, en un carbono no de alquinilo del mismo, R^{45}, alcoxi inferior opcionalmente sustituido con R^{46}, mono-alquilamino, di-alquilamino, cicloalquilamino, cicloalquilalquilo-NH-, heterocicloalquilamino y heterocicloalquilalquilo-NH-;

cada R^{41}, cuando se presenta, se selecciona independientemente del grupo que consiste en halógeno, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, -C(O)-O-R^{47}, -N(H)-C(O)-R^{48}, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior; o dos R^{41} en carbonos adyacentes se combinan para formar un heterocicloalquilo fusionado opcionalmente sustituido con uno o más alquilo inferior;

cada R^{42}, cuando se presenta, se selecciona independientemente del grupo que consiste en alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, -C(O)-O-R^{49}, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior;

cada R^{43}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino;

cada R^{44}, cuando se presenta, es independientemente hidrógeno o alquilo inferior opcionalmente sustituido con uno o más flúor;

cada R^{45}, cuando se presenta, se selecciona independientemente del grupo que consiste en -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino;

cada R^{46}, cuando se presenta, se selecciona independientemente del grupo que consiste en -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino;

cada R^{47}, cuando se presenta, es independientemente hidrógeno o alquilo inferior opcionalmente sustituido con uno o más flúor;

cada R^{48}, cuando se presenta, es independientemente alquilo inferior opcionalmente sustituido con uno o más flúor; y

cada R^{49}, cuando se presenta, es independientemente hidrógeno o alquilo inferior opcionalmente sustituido con uno o más flúor.

4. El compuesto de la modalidad 3, en donde R^{37} es alquilo inferior, alquilo inferior sustituido con flúor o fenilo, opcionalmente sustituido con de 1-3 grupos R^{41}.

5. El compuesto de la modalidad 4, en donde R^{37} es alquilo inferior, alquilo inferior sustituido con flúor o fenilo sustituido con de 1-3 grupos seleccionados de flúor, cloro, -CN, -NO_2, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, -C(O)-O-R^{47} o -N(H)-C(O)-R^{48}.

6. El compuesto de la modalidad 5, en donde R^{37} es alquilo inferior o fenilo sustituido con de 1-2 grupos seleccionados de flúor, cloro, -CN, -NO_2, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior o alcoxi inferior sustituido con flúor.

7. El compuesto de la modalidad 3, en donde R^{38} es H, -F o alquilo inferior sustituido con flúor.

8. El compuesto de la modalidad 3, en donde R^{39} es flúor, cloro, -CN, -OH, -NH_2, alcoxi inferior, alquilo inferior opcionalmente sustituido con uno o más R^{43}, cicloalquilamino, cicloalquilalquilo-NH-, heterocicloalquilamino y heterocicloalquilalquilo-NH-.

9. El compuesto de la modalidad 3, en donde R^{40} es H, alquilo inferior opcionalmente sustituido con uno o más R^{43}, halógeno, alcoxi inferior o –CN.

10. El compuesto de cualquiera de las modalidades 3-9, en donde R^{37} es alquilo inferior o fenilo opcionalmente sustituido con 1-2 miembros seleccionados de CF_3 o halógeno.

11. El compuesto de la modalidad 10, en donde R^{37} es propilo, 2-trifluorometilfenilo, 3-trifluorometilfenilo, 4-trifluorometilfenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo o fenilo 2,5-difluoro-sustituido.

12. El compuesto de la modalidad 11, en donde R^{37} es propilo, 4-trifluorometilfenilo, 2-fluorofenilo, 3-fluorofenilo o fenilo 2,5-difluoro-sustituido.

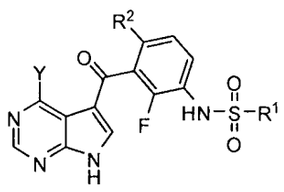
13. El compuesto de cualquiera de las modalidades 3-9, en donde R^{38} es H, F o CF_3.

14. El compuesto de cualquiera de las modalidades 3-9, en donde R^{38} es F.

15. El compuesto de cualquiera de las modalidades 3-9, en donde R^{39} es flúor, cloro, -CN, -OH, -NH_2, alquilo inferior opcionalmente sustituido con flúor, alcoxi inferior, cicloalquilamino, cicloalquilalquilo-NH-, heterocicloalquilamino y heterocicloalquilalquilo-NH-.

16. El compuesto de la modalidad 15, en donde R^{39} es flúor, cloro, -CN, -OH, -NH_2, CH_3, CH_3O-, CF_3, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclopropilmetilo, ciclobutilmetilo, ciclopentilmetilo, ciclohexilmetilo, ciclopropilamino, ciclobutilamino, ciclopentilamino, ciclohexilamino, ciclopropilmetilamino, ciclobutilmetilamino, ciclopentilmetilamino, ciclohexilmetilamino, 2-tetrahidrofuranilamino, 3-tetrahidrofuranilamino o 4-tetrahidropiranilamino.

17. El compuesto de la modalidad 1 o 2, que tiene la Fórmula III:



III

18. El compuesto de cualquiera de las modalidades 1, 2 o 17, en donde X se selecciona del grupo que consiste en –N=, –CH=, -$C(CH_3)$=, -$C(OCH_3)$=, -C(F)=, -C(CN)=, -$C(CH_2OH)$= y –C(Cl)=.

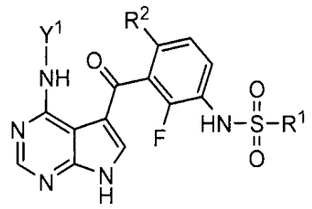
19. El compuesto de cualquiera de las modalidades 1, 2 o 17, en donde X es –N=, –CH=, -$C(CH_3)$=, -C(F)= o -C(CN)=.

20. El compuesto de cualquiera de las modalidades 1, 2 o 17, en donde X es –N=.

21. El compuesto de cualquiera de las modalidades 1, 2 o 17, en donde Y es flúor, cloro, bromo, yodo, alquilo inferior, alcoxi inferior, haloalquilo, CN, -OH, cicloalquilo, -OR^8 o –$NH(R^4)$.

22. El compuesto de cualquiera de las modalidades 1, 2 o 17, en donde Y es CH_3, etilo, metoxi, etioxi, isobutilo, CN, OH, F, Cl, Br, I, NH_2, butioxi, 2-metilpropoxi, 4-tetrahidropiraniloxi, 2-tetrahirofuraniloxi, 3-tetrahirofuraniloxi, alcoxiamino o HO-NH-.

23. El compuesto de las modalidades 1 o 2, que tiene la Fórmula IIIa:



IIIa

en donde Y^1 es alquilo inferior opcionalmente sustituido con de uno a tres R^{11}, cicloalquilo, cicloalquilalquilo, arilo, arilalquilo, heterocicloalquilo, heterocicloalquilalquilo, heteroarilo o heteroarilalquilo, en donde:

(i) el cicloalquilo y cicloalquilalquilo se sustituyen cada uno opcionalmente con de uno a tres R^{12};

(ii) el heterocicloalquilo y heterocicloalquilalquilo se sustituyen cada uno opcionalmente con de uno a tres R^{13};

(iii) el arilo y arilalquilo se sustituyen cada uno opcionalmente con de uno a tres R^{14} opcionalmente, en donde los dos grupos R^{14} adyacentes en el anillo arilo se toman en conjunto para formar un anillo hetero aromático de 5 o 6 miembros que tiene de 1-4 heteroátomos seleccionados de O o N; y

(iv) el heteroarilo y heteroarilalquilo se sustituyen cada uno opcionalmente con de uno a tres R^{15};

24. El compuesto de la modalidad 23, en donde Y^1 se selecciona de alquilo inferior, alquilo inferior sustituido con halógeno, 2-hidroxietilo, ciclopropilamino, ciclobutilo, ciclopropilmetilo, ciclobutilmetilo, ciclopentilo, ciclopentilmetilo, ciclohexilmetilo, ciclohexilo, 2-oxetanilo, 2-oxetanilmetilo, 3-oxetanilo, 3-oxetanilmetilo, 2-tetrahidrofuranilo, 3-tetrahidrofuranilo, 2-tetrahidropiranilo, 3-tetrahidropiranilo, 4-tetrahidropiranilo, 2-tetrahidrofuranilmetilo, 3-tetrahidrofuranilmetilo, 2-tetrahidropiranilmetilo, 3-tetrahidropiranilmetilo, 4-tetrahidropiranilmetilo, 1-metil-2-aziridinilo, 1-metil-2-aziridinilmetilo, 1-metil-2-ażetidinilo, 1-metil-2-azetidinilmetilo, 1-metil-3-azetidinilo, 1-metil-3-azetidinilmetilo, 1-metil-2-pirrolidinilo, 1-metil-2-pirrolidinilmetilo, 1-metil-3-pirrolidinilo, 1-metil-3-pirrolidinilmetilo, 1-metil-2-piperidinilo, 1-metil-2-piperidinilmetilo, 1-metil-3-piperidinilo, 1-metil-3-piperidinilmetilo, 1-metil-4-piperidinilo, 1-metil-4-piperidinilmetilo, 1-metilsulfonil-2-piperidinilo, 1-metilsulfonil-2-piperidinilmetilo, 1-metilsulfonil-3-piperidinilo, 1-metilsulfonil-3-piperidinilmetilo, 1-metilsulfonil-4-piperidinilo, 1-metilsulfonil-4-piperidinilmetilo, 1,1-dioxo-4-tianilo, 1,1-dioxo-4-tianilmetilo, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-bencilo, 2-fluorobencilo, 3-fluorobencilo, 4-fluorobencilo, 2-piridilo, 2-piridilmetilo, 3-piridilo, 3-piridilmetilo, 4-piridilo, 4-piridilmetilo, 2-clorofenilo, 3-clorofenilo, 4-clorofenilo, 2-dimetilaminofenilo, 3-dimetilaminofenilo, 4-dimetilaminofenilo, 2-dimetilaminobencilo, 2-dimetilaminobencilo, 3-dimetilaminobencilo, 4-dimetilaminobencilo, 2-hidoxifenilo, 3-hidoxifenilo, 4-hidoxifenilo, 2-hidroxibencilo, 3-hidroxibencilo, 4-hidroxibencilo, 2-carboxifenilo, 3-carboxifenilo, 4-carboxifenilo, 2-carboxibencilo, 3-carboxibencilo, 4-carboxibencilo, 2-metoxicarbonilfenilo, 3-metoxicarbonilfenilo, 4-metoxicarbonilfenilo, 2-metoxicarbonilbencilo, 3-metoxicarbonilbencilo, 4-metoxicarbonilbencilo, 1-alquil-4-pirazolilo, 1-alquil-4-pirazolilmetilo, 3-piridazinilo, piridazinilmetilo, 4-piridazinilo, 4-piridazinilmetilo, triazolilo, triazolimetilo, tetrazolilo, tetrazolimetilo, 2,1,3,-benzoxadiazolilo, 2,1,3-

benzoxadiazol-5-ilo, 2,1,3,-benzoxadiazolil-metilo, 2,1,3-benzoxadiazol-5ilmetilo, 2,1,3,-benzotiadiazolilo, 2,1,3-benzotiadiazol-5-ilo, 2,1,3,-benzotiadiazolil-metilo, 2,1,3-benzotiadiazol-5ilmetilo, 1H-1,2,4-triazol-5-ilo, 1H-1,2,4-triazol-5-metilo, 2-oxobencimidazol-4-ilo, 2-oxobencimidazol-4-metilo, 2-oxobencimidazol-5-ilo, 2-oxobencimidazol-5-metilo, 1,1,-dioxo-tiolan-3-ilo, 1,1-dioxotiolan-3-metilo, 3-(2-metil-1,2,3,4-tetrazol-5-il)fenilo, 3-(2-metil-1,2,3,4-tetrazol-5-il)bencilo, 3-(5-metil-1,2,3,4-tetrazol-1-il)fenilo, 3-(1,2,4-triazol-5-il)fenilo, 3-(1,2,,4-triazol-5-il)bencilo, 3-3-metil-4H-1,2,4-triazol-5-metilo o 2-(3-metil-4H-1,2,4-triazol-5-il)etilo.

25. El compuesto de cualquiera de las modalidades 17-23 o 24, en donde R^2 es H o F.

26. El compuesto de cualquiera de las modalidades 17-23 o 24, en donde R^1 es alquilo inferior, cicloalquilo opcionalmente sustituido con 1-2 grupos seleccionados de halógeno o alquilo inferior, heterocicloalquilo, heteroarilo opcionalmente sustituido con alquilo inferior o alcoxi inferior, fenilo opcionalmente sustituido con 1-2 sustituyentes seleccionados de alquilo inferior, halógeno, alcoxi inferior, haloalquilo, haloalcoxi o CN.

27. El compuesto de la modalidad 26, en donde R^1 es metilo, propilo, isobutilo, 2-metilpropilo, CF_3, CF_3CH_2-, CHF_2CH_2-, 4-trifluorofenilo, 2-trifluorofenilo, 3-trifluorofenilo, 3,5-dimetilfenilo, 4-propilfenilo, 3-fluoro-4-metoxifenilo, 2-cianofenilo, 3-cianofenilo, 4-cianofenilo, 4-fluoro-3-metoxifenilo, 2,5-difluorofenilo, 2,6-difluorofenilo, 2,4-difluorofenilo, 2-piridilo, 3-piridilo, 5-metoxi-2-piridilo, 3-metoxi-2-piridilo, 4-metoxi-2-piridilo, 6-metil-2-piridilo, 5-metil-2-piridilo, 4-metil-2-piridilo, 3-metil-2-piridilo, dialquilamino, 1-pirrolidinilo, 1-piperidinilo, 4-morfolinilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, 4,4-difluorociclohexilo, 1-metil-4-pirazolilo, 1-etil-4-pirazolilo, 1-metil-3-pirazolilo, 1-etil-3-pirazolilo, 6-metil-3-piridilo, 5-metil-3-piridilo, 4-metil-3-piridilo o 2-metil-3-piridilo.

28. El compuesto de la modalidad 27, en donde R^1 es 2-fluorofenilo, 3-fluorofenilo, 2,5-difluorofenilo o fenilo 4-alquilo inferior-sustituido, en donde el alquilo inferior se sustituye opcionalmente con uno o más flúor.

29. El compuesto de cualquiera de las modalidades 17-22, en donde Y es $-NR^3R^4$, en donde R^3 y R^4 se combinan con el átomo de nitrógeno al cual se unen para formar un anillo de tres a siete miembros que tiene 0-1 heteroátomo adicional seleccionado de O, N o S, en donde los átomos de nitrógeno y azufre se oxidan opcionalmente.

30. El compuesto de la modalidad 29, en donde Y es 1-aziridinilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidinilo, 1-morfolinilo o 1-azepanilo.

31. Un compuesto seleccionado del grupo que consiste en:
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (P-1001),
Ácido propano-1-sulfónico [3-(4-etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (P-1002),
ácido 2-Metil-propano-1-sulfónico [2,4-difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-

amida (P-1003),
ácido 2-Metil-propano-1-sulfónico [2,4-difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (P-1004),
N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida (P-1005),
N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (P-1006),
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida (P-1007),
N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida (P-1008),
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida (P-1009),
N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida (P-1010),
N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (P-1012),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-isobutil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (P-1014),
N-[2,4-Difluoro-3-(4-isobutil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (P-1015),
N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (P-1016),
ácido 6-Metoxi-piridin-3-sulfónico [2,4-difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (P-1018),
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida (P-1019),
N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-iloxi)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (P-1021),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (P-1022),
N-[3-(4-Ciano-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (P-1023),
N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3,5-dimetil-bencenosulfonamida (P-1025),
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3,5-dimetil-bencenosulfonamida (P-1027),
N-[2,4-Difluoro-3-(4-isobutoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (P-1028),
N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (P-1029),

N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida (P-1030),
Ácido propano-1-sulfónico [3-(4-cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (P-1033),
N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (P-1034),
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-fluoro-4-metoxi-bencenosulfonamida (P-1036),
N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (P-1038),
N-[3-(4-Ciclopropilmetoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (P-1053),
N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (P-1070),
N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (P-1071),
N-[3-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (P-1107),
N-[3-(4-Ciclopropilmetoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (P-1181),
N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (P-1182),
N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (P-1183),
N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (P-1184),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-amida (P-2015),
N-[2,4-Difluoro-3-(4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (P-2016),
N-[2,4-Difluoro-3-(4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-bencenosulfonamida (P-2017), y

cualquier sal farmacéuticamente aceptable de los mismos.

32. Una composición que comprende un compuesto de cualquiera de las modalidades 1-31 y un excipiente o portador farmacéuticamente aceptable.

33. Una composición farmacéutica que comprende un compuesto de cualquiera de las modalidades 1-31 y otro fármaco.

34. Un kit que comprende un compuesto de acuerdo con cualquiera de las modalidades 1-31 o una composición de acuerdo con la modalidad 32 o 33.

35. Un método para tratar una enfermedad o padecimiento mediado por proteína cinasa Raf en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las modalidades 1-31 o una composición de las modalidades 32 o 33.

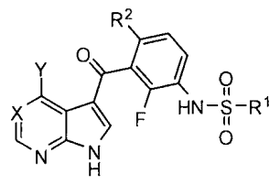
36. Un método para tratar una enfermedad o padecimiento mediado por proteína cinasa Raf en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las modalidades 1-31 y otro fármaco o una sal farmacéuticamente aceptable del mismo.

37. El método de la modalidad 35 o 36, en donde la enfermedad o padecimiento se selecciona del grupo que consiste en demencia vascular, lesión en cabeza, lesión en médula espinal, enfermedad de Alzheimer (AD), enfermedad de Parkinson, ataques y epilepsia; enfermedades neoplásicas incluyendo, pero sin limitarse a, melanoma, glioma, sarcoma, carcinoma (por ejemplo, gastrointestinal, de hígado, conducto biliar (colangiocarcinoma), colorectal, pulmón, mama, pancreático, tiroideo, renal, ovárico, próstata), linfoma (por ejemplo, linfoma histiocítico) neurofibromatosis, leucemia mieloide aguda, síndrome mielodisplásico, leucemia, angiogénesis tumoral, tumores neuroendocrinos tales como cáncer de tiroides medular, carcinoide, cáncer de pulmón de células pequeñas, sarcoma de Kaposi, y feocromocitoma; dolor de origen neuropático o inflamatorio, incluyendo, pero sin limitarse a, dolor agudo, dolor crónico, dolor relacionado con cáncer, y migraña; enfermedades cardiovasculares incluyendo, pero sin limitarse a, falla cardiaca, apoplejía isquémica, hipertrofia cardiaca, trombosis (por ejemplo, síndromes de microangiopatía trombótica), ateroesclerosis, y lesión por reperfusión; inflamación y/o proliferación incluyendo, pero sin limitarse a, psoriasis, eczema, artritis y enfermedades y padecimientos autoinmunes, osteoartritis, endometriosis, cicatrización, restenosis vascular, trastornos fibróticos, artritis reumatoide, enfermedad intestinal inflamatoria (IBD); enfermedades por inmunodeficiencias, incluyendo, pero sin limitarse a, rechazo de transplantes de órganos, enfermedad injerto versus huésped, y sarcoma de Kaposi asociado con HIV; enfermedades renales, quísticas, o prostáticas, incluyendo, pero sin limitarse a, nefropatía diabética, enfermedad renal poliquística, nefroesclerosis, glomerulonefritis, hiperplasia de próstata, enfermedad de hígado poliquístico, esclerosis tuberosa, enfermedad de Von Hippel Lindau, enfermedad renal medular quística, nefronoftisis, y fibrosis quística; trastornos metabólicos, incluyendo, pero sin limitarse a, obesidad; infección, incluyendo, pero sin limitarse a, *Helicobacter pylori*, virus de Hepatitis e Influenza, fiebre, HIV, y septicemia; enfermedades pulmonares incluyendo, pero sin limitarse a, enfermedad pulmonar obstructiva crónica (COPD) y síndrome de insuficiencia respiratoria aguda (ARDS); enfermedades genéticas del desarrollo, incluyendo, pero sin limitarse a, síndrome de Noonan, síndrome de Costello, (síndrome faciocutaneoesquelético), síndrome LEOPARD, síndrome cardio-faciocutáneo (CFC), y anormalidades del síndrome de crestas neurales que provocan enfermedades cardiovasculares, esqueléticas, intestinales, de piel, cabello y endocrinas; y enfermedades asociadas con regeneración o degeneración muscular, incluyendo, pero sin limitarse a, sarcopenia, distrofias musculares (incluyendo, pero sin limitarse a,

Distrofias de Duchenne, Becker, Emery-Dreifuss, de Cintura Pélvica, Facioescapulohumeral, Miotónica, Oculofaríngea, Distal y Muscular Congénita), enfermedades de neuronas motoras (incluyendo, pero sin limitarse a, esclerosis lateral amiotrófica, atrofia muscular espinal progresiva infantil, atrofia muscular espinal intermedia, atrofia muscular espinal juvenil, atrofia muscular bulbar espinal, y atrofia muscular espinal adulta), miopatías inflamatorias (incluyendo, pero sin limitarse a, dermatomiositis, polimiositis, y miositis por cuerpos de inclusión), enfermedades de la placa neuromuscular (incluyendo, pero sin limitarse a, miastenia grave, síndrome de Lambert-Eaton, y síndrome miasténico congénito), miopatías debido a anormalidades endocrinas (incluyendo, pero sin limitarse a, miopatía hipertiroidea y miopatía hipotiroidea) enfermedades de nervios periféricos (incluyendo, pero sin limitarse a, enfermedad de Charcot Marie Tooth, enfermedad de Dejerine-Sottas, y ataxia de Friedreich), otras miopatías (incluyendo, pero sin limitarse a, miotonía congénita, paramiotonía congénita, enfermedad de núcleo central, miopatía nemalínica, miopatía miotubular, y parálisis periódica), y enfermedades metabólicas de músculo (incluyendo, pero sin limitarse a, deficiencia de fosforilasa, deficiencia de maltasa ácida, deficiencia de fosfofructocinasa, deficiencia de enzima de desconexión, miopatía mitocondrial, deficiencia de carnitina, deficiencia de carnitina palmatilo transferasa, deficiencia de fosfoglicerato cinasa, deficiencia de fosfoglicerato mutasa, deficiencia de lactato deshidrogenasa, y deficiencia de mioadenilato desaminasa).

38. El método de la modalidad 37, en donde la enfermedad o padecimiento se selecciona del grupo que consiste en melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, cáncer colorrectal, cáncer de tiroides, cáncer de pulmón, cáncer ovárico, cáncer de próstata, cáncer de hígado, cáncer de vesícula biliar, tumores de estroma gastrointestinal, cáncer del tracto biliar, cáncer testicular y colangiocarcinoma.

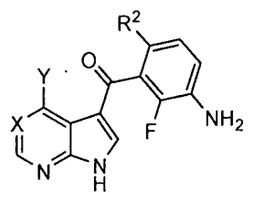
39. Un método para preparar un compuesto de la Fórmula I de acuerdo con la modalidad 1



I

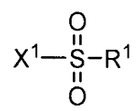
el método comprende:

poner en contacto un compuesto de la Fórmula IVc:



IVc

con un compuesto de la Fórmula V:



V

bajo condiciones suficientes para formar el compuesto de la Fórmula I, en donde:

X^1 es un halógeno.

40. El método de la modalidad 39, en donde X es –N=, –CH=, -C(CH_3)=, -C(OCH_3)=, -C(F)=, -C(CN)=, -C(CH_2OH)= o –C(Cl)=.

41. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31 o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar cualquier enfermedad o padecimiento mediado por proteína cinasa Raf en un sujeto en necesidad de ello.

42. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31 o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para su uso en el tratamiento de una enfermedad o padecimiento mediado por proteína cinasa Raf en un sujeto en necesidad de ello.

43. Un método para tratar una o más indicaciones seleccionadas del grupo que consiste en melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, cáncer colorrectal, cáncer de tiroides, cáncer de pulmón, cáncer ovárico, cáncer de próstata, cáncer de hígado, cáncer de vesícula biliar, tumores de estroma gastrointestinal, cáncer del tracto biliar, cáncer testicular y colangiocarcinoma en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

44. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar una o más indicaciones seleccionadas del grupo que consiste en melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, cáncer colorrectal, cáncer de tiroides, cáncer de pulmón, cáncer ovárico, cáncer de próstata, cáncer de hígado, cáncer de vesícula biliar, tumores de estroma gastrointestinal, cáncer del tracto biliar, cáncer testicular y colangiocarcinoma en un sujeto en necesidad de ello.

45. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de una o más indicaciones seleccionadas del grupo que consiste en melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, cáncer colorrectal, cáncer de tiroides, cáncer de pulmón, cáncer ovárico, cáncer de próstata, cáncer de hígado, cáncer de vesícula biliar, tumores de estroma gastrointestinal, cáncer del tracto biliar, cáncer testicular y colangiocarcinoma en un sujeto en necesidad de ello.

46. Un método para tratar melanoma en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las

Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

47. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar melanoma en un sujeto en necesidad de ello.

48. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de melanoma en un sujeto en necesidad de ello.

49. Un método para tratar glioma en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

50. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar glioma en un sujeto en necesidad de ello.

51. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para glioma en un sujeto en necesidad de ello.

52. Un método para tratar glioblastoma multiforme en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

53. El uso de un compuesto de acuerdo con cualquiera de 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar glioblastoma multiforme en un sujeto en necesidad de ello.

54. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de glioblastoma multiforme en un sujeto en necesidad de ello.

55. Un método para tratar astrocitoma pilocítico, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

56. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33

para la preparación de un medicamento para tratar astrocitoma pilocítico en un sujeto en necesidad de ello.

57. Un compuesto de acuerdo con cualquiera de las Modalidades 11-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de astrocitoma pilocítico en un sujeto en necesidad de ello.

58. Un método para tratar cáncer colorrectal que comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

59. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar cáncer colorrectal en un sujeto en necesidad de ello.

60. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de cáncer colorrectal en un sujeto en necesidad de ello.

61. Un método para tratar cáncer de tiroides en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

62. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar cáncer de tiroides en un sujeto en necesidad de ello.

63. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de cáncer de tiroides en un sujeto en necesidad de ello.

64. Un método para tratar cáncer de pulmón en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

65. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar cáncer de pulmón en un sujeto en necesidad de ello.

66. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de cáncer de pulmón en un sujeto en necesidad de ello.

67. Un método para tratar cáncer ovárico en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

68. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar cáncer ovárico en un sujeto en necesidad de ello.

69. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de cáncer ovárico en un sujeto en necesidad de ello.

70. Un método para tratar cáncer de próstata en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

71. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar cáncer de próstata en un sujeto en necesidad de ello.

72. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de cáncer de próstata en un sujeto en necesidad de ello.

73. Un método para tratar cáncer de hígado en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

74. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar cáncer de hígado en un sujeto en necesidad de ello.

75. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de cáncer de hígado en un sujeto en necesidad de ello.

76. Un método para tratar cáncer de vesícula biliar en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

77. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar cáncer de vesícula biliar en un sujeto en necesidad de ello.

78. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de cáncer de vesícula biliar en un sujeto en necesidad de ello.

79. Un método para tratar tumores de estroma gastrointestinal en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

80. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar tumores de estroma gastrointestinal en un sujeto en necesidad de ello.

81. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de tumores de estroma gastrointestinal en un sujeto en necesidad de ello.

82. Un método para tratar cáncer del tracto biliar en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

83. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar cáncer del tracto biliar en un sujeto en necesidad de ello.

84. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de cáncer del tracto biliar en un sujeto en necesidad de ello.

85. Un método para tratar colangiocarcinoma en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las

Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

86. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar colangiocarcinoma en un sujeto en necesidad de ello.

87. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de colangiocarcinoma en un sujeto en necesidad de ello.

88. Un método para tratar una o más indicaciones seleccionadas del grupo que consiste en dolor agudo, dolor crónico, y enfermedad renal poliquística en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

89. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar una o más indicaciones seleccionadas del grupo que consiste en dolor agudo, dolor crónico, y enfermedad renal poliquística en un sujeto en necesidad de ello.

90. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de una o más indicaciones seleccionadas del grupo que consiste en dolor agudo, dolor crónico, y enfermedad renal poliquística en un sujeto en necesidad de ello.

91. Un método para tratar dolor agudo en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

92. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar dolor agudo en un sujeto en necesidad de ello.

93. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de dolor agudo en un sujeto en necesidad de ello.

94. Un método para tratar dolor crónico en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

95. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar dolor crónico en un sujeto en necesidad de ello.

96. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de dolor crónico en un sujeto en necesidad de ello.

97. Un método para tratar la enfermedad renal poliquística en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

98. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar la enfermedad renal poliquística en un sujeto en necesidad de ello.

99. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de la enfermedad renal poliquística en un sujeto en necesidad de ello.

100. Un método para tratar una o más indicaciones seleccionadas del grupo que consiste en demencia vascular, lesión en cabeza, lesión en médula espinal, enfermedad de Alzheimer (AD), enfermedad de Parkinson, ataques y epilepsia; enfermedades neoplásicas incluyendo, pero sin limitarse a, melanoma, glioma, sarcoma, carcinoma (por ejemplo, gastrointestinal, de hígado, conducto biliar (colangiocarcinoma), colorectal, pulmón, mama, pancreático, tiroideo, renal, ovárico, próstata), linfoma (por ejemplo, linfoma histiocítico) neurofibromatosis, leucemia mieloide aguda, síndrome mielodisplásico, leucemia, angiogénesis tumoral, tumores neuroendocrinos tales como cáncer de tiroides medular, carcinoide, cáncer de pulmón de células pequeñas, sarcoma de Kaposi, y feocromocitoma; dolor de origen neuropático o inflamatorio, incluyendo, pero sin limitarse a, dolor agudo, dolor crónico, dolor relacionado con cáncer, y migraña; enfermedades cardiovasculares incluyendo, pero sin limitarse a, falla cardiaca, apoplejía isquémica, hipertrofia cardiaca, trombosis (por ejemplo, síndromes de microangiopatía trombótica), ateroesclerosis, y lesión por reperfusión; inflamación y/o proliferación incluyendo, pero sin limitarse a, psoriasis, eczema, artritis y enfermedades y padecimientos autoinmunes, osteoartritis, endometriosis, cicatrización, restenosis vascular, trastornos fibróticos, artritis reumatoide, enfermedad intestinal inflamatoria (IBD); enfermedades por inmunodeficiencias, incluyendo, pero sin limitarse a, rechazo de transplantes de órganos, enfermedad injerto versus huésped, y sarcoma de Kaposi asociado con HIV; enfermedades renales, quísticas, o prostáticas, incluyendo, pero sin limitarse a, nefropatía diabética, enfermedad renal poliquística, nefroesclerosis, glomerulonefritis, hiperplasia de próstata, enfermedad de hígado poliquístico, esclerosis tuberosa, enfermedad de Von Hippel Lindau, enfermedad renal medular quística, nefronoftisis, y fibrosis quística; trastornos metabólicos, incluyendo, pero sin limitarse a, obesidad; infección, incluyendo, pero sin limitarse a, *Helicobacter pylori*, virus de Hepatitis c

Influenza, fiebre, HIV, y septicemia; enfermedades pulmonares incluyendo, pero sin limitarse a, enfermedad pulmonar obstructiva crónica (COPD) y síndrome de insuficiencia respiratoria aguda (ARDS); enfermedades genéticas del desarrollo, incluyendo, pero sin limitarse a, síndrome de Noonan, síndrome de Costello, (síndrome faciocutaneoesquelético), síndrome LEOPARD, síndrome cardio-faciocutáneo (CFC), y anormalidades del síndrome de crestas neurales que provocan enfermedades cardiovasculares, esqueléticas, intestinales, de piel, cabello y endocrinas; y enfermedades asociadas con regeneración o degeneración muscular, incluyendo, pero sin limitarse a, sarcopenia, distrofias musculares (incluyendo, pero sin limitarse a, Distrofias de Duchenne, Becker, Emery-Dreifuss, de Cintura Pélvica, Facioescapulohumeral, Miotónica, Oculofaríngea, Distal y Muscular Congénita), enfermedades de neuronas motoras (incluyendo, pero sin limitarse a, esclerosis lateral amiotrófica, atrofia muscular espinal progresiva infantil, atrofia muscular espinal intermedia, atrofia muscular espinal juvenil, atrofia muscular bulbar espinal, y atrofia muscular espinal adulta), miopatías inflamatorias (incluyendo, pero sin limitarse a, dermatomiositis, polimiositis, y miositis por cuerpos de inclusión), enfermedades de la placa neuromuscular (incluyendo, pero sin limitarse a, miastenia grave, síndrome de Lambert-Eaton, y síndrome miasténico congénito), miopatías debido a anormalidades endocrinas (incluyendo, pero sin limitarse a, miopatía hipertiroidea y miopatía hipotiroidea) enfermedades de nervios periféricos (incluyendo, pero sin limitarse a, enfermedad de Charcot Marie Tooth, enfermedad de Dejerine-Sottas, y ataxia de Friedreich), otras miopatías (incluyendo, pero sin limitarse a, miotonía congénita, paramiotonía congénita, enfermedad de núcleo central, miopatía nemalínica, miopatía miotubular, y parálisis periódica), y enfermedades metabólicas de músculo (incluyendo, pero sin limitarse a, deficiencia de fosforilasa, deficiencia de maltasa ácida, deficiencia de fosfofructocinasa, deficiencia de enzima de desconexión, miopatía mitocondrial, deficiencia de carnitina, deficiencia de carnitina palmatilo transferasa, deficiencia de fosfoglicerato cinasa, deficiencia de fosfoglicerato mutasa, deficiencia de lactato deshidrogenasa, y deficiencia de mioadenilato desaminasa) en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

101. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar una o más indicaciones seleccionadas del grupo que consiste en demencia vascular, lesión en cabeza, lesión en médula espinal, enfermedad de Alzheimer (AD), enfermedad de Parkinson, ataques y epilepsia; enfermedades neoplásicas incluyendo, pero sin limitarse a, melanoma, glioma, sarcoma, carcinoma (por ejemplo, gastrointestinal, de hígado, conducto biliar (colangiocarcinoma), colorectal, pulmón, mama, pancreático, tiroideo, renal, ovárico, próstata), linfoma (por ejemplo, linfoma histiocítico) neurofibromatosis, leucemia mieloide aguda, síndrome mielodisplásico, leucemia, angiogénesis tumoral, tumores neuroendocrinos tales como cáncer de tiroides medular, carcinoide, cáncer de pulmón de células pequeñas, sarcoma de Kaposi, y feocromocitoma; dolor de origen neuropático o inflamatorio, incluyendo, pero sin limitarse a, dolor agudo, dolor crónico, dolor relacionado con cáncer, y migraña; enfermedades cardiovasculares incluyendo, pero sin limitarse a, falla cardiaca, apoplejía isquémica, hipertrofia cardiaca, trombosis (por ejemplo, síndromes de microangiopatía

trombótica), ateroesclerosis, y lesión por reperfusión; inflamación y/o proliferación incluyendo, pero sin limitarse a, psoriasis, eczema, artritis y enfermedades y padecimientos autoinmunes, osteoartritis, endometriosis, cicatrización, restenosis vascular, trastornos fibróticos, artritis reumatoide, enfermedad intestinal inflamatoria (IBD); enfermedades por inmunodeficiencias, incluyendo, pero sin limitarse a, rechazo de transplantes de órganos, enfermedad injerto versus huésped, y sarcoma de Kaposi asociado con HIV; enfermedades renales, quísticas, o prostáticas, incluyendo, pero sin limitarse a, nefropatía diabética, enfermedad renal poliquística, nefroesclerosis, glomerulonefritis, hiperplasia de próstata, enfermedad de hígado poliquístico, esclerosis tuberosa, enfermedad de Von Hippel Lindau, enfermedad renal medular quística, nefronoftisis, y fibrosis quística; trastornos metabólicos, incluyendo, pero sin limitarse a, obesidad; infección, incluyendo, pero sin limitarse a, *Helicobacter pylori*, virus de Hepatitis e Influenza, fiebre, HIV, y septicemia; enfermedades pulmonares incluyendo, pero sin limitarse a, enfermedad pulmonar obstructiva crónica (COPD) y síndrome de insuficiencia respiratoria aguda (ARDS); enfermedades genéticas del desarrollo, incluyendo, pero sin limitarse a, síndrome de Noonan, síndrome de Costello, (síndrome faciocutaneoesquelético), síndrome LEOPARD, síndrome cardio-faciocutáneo (CFC), y anormalidades del síndrome de crestas neurales que provocan enfermedades cardiovasculares, esqueléticas, intestinales, de piel, cabello y endocrinas; y enfermedades asociadas con regeneración o degeneración muscular, incluyendo, pero sin limitarse a, sarcopenia, distrofias musculares (incluyendo, pero sin limitarse a, Distrofias de Duchenne, Becker, Emery-Dreifuss, de Cintura Pélvica, Facioescapulohumeral, Miotónica, Oculofaríngea, Distal y Muscular Congénita), enfermedades de neuronas motoras (incluyendo, pero sin limitarse a, esclerosis lateral amiotrófica, atrofia muscular espinal progresiva infantil, atrofia muscular espinal intermedia, atrofia muscular espinal juvenil, atrofia muscular bulbar espinal, y atrofia muscular espinal adulta), miopatías inflamatorias (incluyendo, pero sin limitarse a, dermatomiositis, polimiositis, y miositis por cuerpos de inclusión), enfermedades de la placa neuromuscular (incluyendo, pero sin limitarse a, miastenia grave, síndrome de Lambert-Eaton, y síndrome miasténico congénito), miopatías debido a anormalidades endocrinas (incluyendo, pero sin limitarse a, miopatía hipertiroidea y miopatía hipotiroidea) enfermedades de nervios periféricos (incluyendo, pero sin limitarse a, enfermedad de Charcot Marie Tooth, enfermedad de Dejerine-Sottas, y ataxia de Friedreich), otras miopatías (incluyendo, pero sin limitarse a, miotonía congénita, paramiotonía congénita, enfermedad de núcleo central, miopatía nemalínica, miopatía miotubular, y parálisis periódica), y enfermedades metabólicas de músculo (incluyendo, pero sin limitarse a, deficiencia de fosforilasa, deficiencia de maltasa ácida, deficiencia de fosfofructocinasa, deficiencia de enzima de desconexión, miopatía mitocondrial, deficiencia de carnitina, deficiencia de carnitina palmatilo transferasa, deficiencia de fosfoglicerato cinasa, deficiencia de fosfoglicerato mutasa, deficiencia de lactato deshidrogenasa, y deficiencia de mioadenilato desaminasa) en un sujeto en necesidad de ello.

102. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de una o más indicaciones seleccionadas del grupo que consiste en demencia vascular, lesión en cabeza, lesión en médula espinal, enfermedad de Alzheimer (AD), enfermedad de Parkinson, ataques y epilepsia; enfermedades neoplásicas incluyendo, pero sin limitarse a, melanoma, glioma, sarcoma, carcinoma (por ejemplo, gastrointestinal, de hígado, conducto biliar (colangiocarcinoma), colorectal,

pulmón, mama, pancreático, tiroideo, renal, ovárico, próstata), linfoma (por ejemplo, linfoma histiocítico) neurofibromatosis, leucemia mieloide aguda, síndrome mielodisplásico, leucemia, angiogénesis tumoral, tumores neuroendocrinos tales como cáncer de tiroides medular, carcinoide, cáncer de pulmón de células pequeñas, sarcoma de Kaposi, y feocromocitoma; dolor de origen neuropático o inflamatorio, incluyendo, pero sin limitarse a, dolor agudo, dolor crónico, dolor relacionado con cáncer, y migraña; enfermedades cardiovasculares incluyendo, pero sin limitarse a, falla cardiaca, apoplejía isquémica, hipertrofia cardiaca, trombosis (por ejemplo, síndromes de microangiopatía trombótica), ateroesclerosis, y lesión por reperfusión; inflamación y/o proliferación incluyendo, pero sin limitarse a, psoriasis, eczema, artritis y enfermedades y padecimientos autoinmunes, osteoartritis, endometriosis, cicatrización, restenosis vascular, trastornos fibróticos, artritis reumatoide, enfermedad intestinal inflamatoria (IBD); enfermedades por inmunodeficiencias, incluyendo, pero sin limitarse a, rechazo de transplantes de órganos, enfermedad injerto versus huésped, y sarcoma de Kaposi asociado con HIV; enfermedades renales, quísticas, o prostáticas, incluyendo, pero sin limitarse a, nefropatía diabética, enfermedad renal poliquística, nefroesclerosis, glomerulonefritis, hiperplasia de próstata, enfermedad de hígado poliquístico, esclerosis tuberosa, enfermedad de Von Hippel Lindau, enfermedad renal medular quística, nefronoftisis, y fibrosis quística; trastornos metabólicos, incluyendo, pero sin limitarse a, obesidad; infección, incluyendo, pero sin limitarse a, *Helicobacter pylori*, virus de Hepatitis e Influenza, fiebre, HIV, y septicemia; enfermedades pulmonares incluyendo, pero sin limitarse a, enfermedad pulmonar obstructiva crónica (COPD) y síndrome de insuficiencia respiratoria aguda (ARDS); enfermedades genéticas del desarrollo, incluyendo, pero sin limitarse a, síndrome de Noonan, síndrome de Costello, (síndrome faciocutaneoesquelético), síndrome LEOPARD, síndrome cardio-faciocutáneo (CFC), y anormalidades del síndrome de crestas neurales que provocan enfermedades cardiovasculares, esqueléticas, intestinales, de piel, cabello y endocrinas; y enfermedades asociadas con regeneración o degeneración muscular, incluyendo, pero sin limitarse a, sarcopenia, distrofias musculares (incluyendo, pero sin limitarse a, Distrofias de Duchenne, Becker, Emery-Dreifuss, de Cintura Pélvica, Facioescapulohumeral, Miotónica, Oculofaríngea, Distal y Muscular Congénita), enfermedades de neuronas motoras (incluyendo, pero sin limitarse a, esclerosis lateral amiotrófica, atrofia muscular espinal progresiva infantil, atrofia muscular espinal intermedia, atrofia muscular espinal juvenil, atrofia muscular bulbar espinal, y atrofia muscular espinal adulta), miopatías inflamatorias (incluyendo, pero sin limitarse a, dermatomiositis, polimiositis, y miositis por cuerpos de inclusión), enfermedades de la placa neuromuscular (incluyendo, pero sin limitarse a, miastenia grave, síndrome de Lambert-Eaton, y síndrome miasténico congénito), miopatías debido a anormalidades endocrinas (incluyendo, pero sin limitarse a, miopatía hipertiroidea y miopatía hipotiroidea) enfermedades de nervios periféricos (incluyendo, pero sin limitarse a, enfermedad de Charcot Marie Tooth, enfermedad de Dejerine-Sottas, y ataxia de Friedreich), otras miopatías (incluyendo, pero sin limitarse a, miotonía congénita, paramiotonía congénita, enfermedad de núcleo central, miopatía nemalínica, miopatía miotubular, y parálisis periódica), y enfermedades metabólicas de músculo (incluyendo, pero sin limitarse a, deficiencia de fosforilasa, deficiencia de maltasa ácida, deficiencia de fosfofructocinasa, deficiencia de enzima de desconexión, miopatía mitocondrial, deficiencia de carnitina, deficiencia de carnitina palmatilo transferasa, deficiencia de fosfoglicerato cinasa, deficiencia de fosfoglicerato mutasa, deficiencia de lactato deshidrogenasa, y deficiencia de mioadenilato desaminasa) en un sujeto en necesidad de ello.

103. Un método para tratar cáncer testicular en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

104. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar cáncer testicular en un sujeto en necesidad de ello.

105. Un compuesto de acuerdo con cualquiera de las Modalidades 11-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento de cáncer testicular en un sujeto en necesidad de ello.

106. Un método para tratar el síndrome de Noonan en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

107. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar el síndrome de Noonan en un sujeto en necesidad de ello.

108. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento del síndrome de Noonan en un sujeto en necesidad de ello.

109. Un método para tratar el síndrome cardio-faciocutáneo (CFC) en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una cantidad efectiva de una composición de acuerdo con cualquiera de las Modalidades 32 o 33.

110. El uso de un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para la preparación de un medicamento para tratar el síndrome cardio-faciocutáneo (CFC) en un sujeto en necesidad de ello.

111. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 para el tratamiento del síndrome cardio-faciocutáneo (CFC) en un sujeto en necesidad de ello.

112. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 en donde el compuesto es un pan inhibidor de Raf.

113. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 en donde el compuesto es un inhibidor de la actividad de Ras.

114. Un compuesto de acuerdo con cualquiera de las Modalidades 1-31, un compuesto listado en la Tabla I o Tabla II, o una composición de acuerdo con cualquiera de las Modalidades 32 o 33 en donde el compuesto es un pan inhibidor de Raf y un inhibidor de la actividad de Ras.

115. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 1 μM.

116. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 100 nM.

117. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 20 nM.

118. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 1 nM.

119. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 1 μM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

120. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 100 nM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

121. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 20 nM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

122. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras con una IC_{50} de menos de 1 nM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

123. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante en N-Ras con una IC_{50} de menos de 1 μM.

124. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante en N-Ras con una IC_{50} de menos de 100 nM.

125. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante en N-Ras con una IC_{50} de menos de 20 nM.

126. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante en N-Ras con una IC_{50} de menos de 1 nM.

127. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante en N-Ras con una IC_{50} de menos de 1 μM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

128. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante en N-Ras con una IC_{50} de menos de 100 nM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

129. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante en N-Ras con una IC_{50} de menos de 20 nM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

120. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante en N-Ras con una IC_{50} de menos de 1 nM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

121. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras seleccionada del grupo que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298 con una IC_{50} de menos de 1 μM.

122. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras seleccionada del grupo

que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298 con una IC_{50} de menos de 100 nM.

123. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras seleccionada del grupo que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298 con una IC_{50} de menos de 20 nM.

124. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras seleccionada del grupo que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298 con una IC_{50} de menos de 1 nM.

125. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras seleccionada del grupo que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298 con una IC_{50} de menos de 1 μM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

126. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras seleccionada del grupo que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298 con una IC_{50} de menos de 100 nM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

127. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras seleccionada del grupo que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298 con una IC_{50} de menos de 20 nM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

128. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de una línea celular mutante de Ras seleccionada del grupo que consiste en M244, M202, M207, SK-MEL-2, SK-MEL-173, e IPC298 con una IC_{50} de menos de 1 nM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

129. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de células IPC298 con una IC_{50} de menos de 1 μM.

130. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de células IPC298 con una IC_{50} de menos de 100 nM.

131. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de células IPC298 con una IC_{50} de menos de 20 nM.

132. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de células IPC298 con una IC_{50} de menos de 1 nM.

133. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de células IPC298 con una IC_{50} de menos de 1 μM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

134. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de células IPC298 con una IC_{50} de menos de 100 nM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

135. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de células IPC298 con una IC_{50} de menos de 20 nM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

136. Un compuesto o composición de acuerdo con cualquiera de las modalidades precedentes, en donde el compuesto inhibe la proliferación de células IPC298 con una IC_{50} de menos de 1 nM y en donde el compuesto es un pan inhibidor de Raf que tiene una IC_{50} de menos de 500 nM en ensayos de actividad para cada una de las proteína cinasas B-Raf, c-Raf-1 y B-Raf V600E.

EJEMPLOS

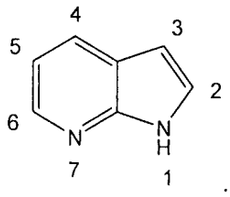
[0207] Ejemplos relacionados con la presente invención se describen a continuación. En la mayoría de los casos, pueden utilizarse técnicas alternativas. Los ejemplos pretenden ser ilustrativos y no limitantes ni restrictivos para el alcance de la invención. Por ejemplo, en casos donde se preparan compuestos adicionales al seguir un protocolo de un Esquema para un compuesto particular, se entiende que las condiciones pueden variar, por ejemplo, cualquiera de los solventes, tiempos de reacción, reactivos, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse al emplear solventes, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares alternos, dado que se encuentran disponibles fácilmente para un experto en la técnica. En algunos ejemplos, el resultado de la espectrometría de masas indicado para un compuesto puede tener más de un valor debido a la distribución de isótopos de un átomo en la molécula, tal como un compuesto que tiene un sustituyente bromo o cloro.

[0208] A menos que se indique específicamente de otra manera, la enumeración de las Fórmulas y enumeración de grupos R utilizados en los siguientes ejemplos no se relaciona con tal enumeración en otras secciones de esta solicitud. Los reactivos y solventes utilizados en estos ejemplos pueden sustituirse fácilmente con alternativas apropiadas como se conocen en la técnica, y el aislamiento de los productos se

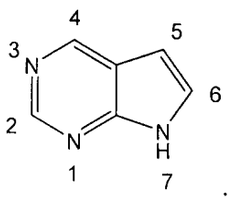
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logra fácilmente por métodos conocidos en la técnica, incluyendo, pero sin limitarse a, extracción, cristalización, y métodos cromatográficos.

[0209] La numeración del anillo para la 1H-pirrolo[2,3-b]piridina en los siguientes Ejemplos es como sigue:



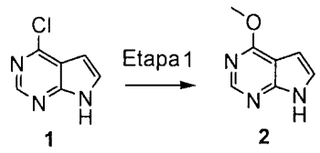
[0210] La numeración del anillo para la 7H-pirrolo[2,3-d]pirimidina en los siguientes Ejemplos es como sigue:



Ejemplo 1: Síntesis de compuestos de 7H-pirrolo[2,3-d]pirimidina.

[0211] La 4-metoxi-7H-pirrolo[2,3-d]pirimidina **2** se prepara en una etapa a partir de 4-cloro-7H-pirrolo[2,3-d]pirimidina **1** como se muestra en el Esquema 1.

Esquema 1

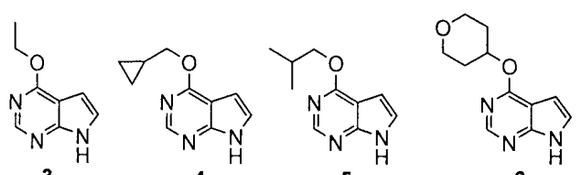


1 **2**

Etapa 1 – Preparación de 4-metoxi-7H-pirrolo[2,3-d]pirimidina (2):

[0212] A 4-cloro-7H-pirrolo[2,3-d]pirimidina (**1**, 3.5 g, 23.0 mmol) en 70 ml de metanol, se agrega hidróxido de potasio (2.3 g, 41.0 mmol) y la reacción se agita a 60 °C durante la noche, entonces se vierte en agua y se extrae con etil acetato. La capa orgánica se separa y se seca sobre sulfato de sodio, se filtra y el filtrado se concentra bajo vacío para proporcionar el compuesto deseado (**2**, 3.20 g).

[0213] 4-etoxi-7H-pirrolo[2,3-d]pirimidina **3**, 4-ciclopropilmetoxi-7H-pirrolo[2,3-d]pirimidina **4**, 4-isobutoxi-7H-pirrolo[2,3-d]pirimidina **5**, y 4-(tetrahidro-piran-4-iloxi)-7H-pirrolo[2,3-d]pirimidina **6**,

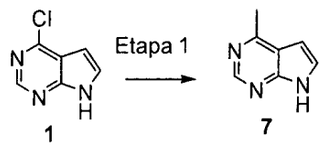


3 , **4** , **5** , y **6** ,

se preparan al seguir el protocolo del Esquema 1, al reemplazar metanol con etanol, ciclopropil-metanol, alcohol isobutílico, y tetrahidro-piran-4-ol, respectivamente. MS (ESI) $[M+H^+]^+$ = 164.9 (**3**); 190.1 (**4**); 192.1 (**5**); y 220.1 (**6**).

[0214] La 4-metil-7H-pirrolo[2,3-d]pirimidina **7** se sintetiza en una etapa a partir de 4-cloro-7H-pirrolo[2,3-d]pirimidina **1** como se muestra en el Esquema 1a.

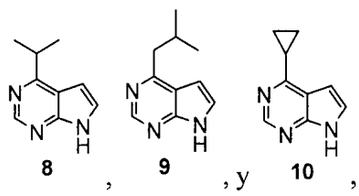
Esquema 1a



Etapa 1 – Preparación de 4-metil-7H-pirrolo[2,3-d]pirimidina (7):

[0215] En un matraz de fondo redondo el catalizador complejo [1,1'-bis(difenilfosfino)ferroceno] dicloropaladio(II), 1:1 con diclorometano (70.0 mg, 0.09 mmol), se coloca bajo nitrógeno con 15 ml de tolueno en conjunto con una barra de agitación. Una suspensión de 4-cloro-7H-pirrolo[2,3-d]pirimidina (**1**, 1.47 g, 9.57 mmol) en 15 ml de tolueno se agrega a temperatura ambiente. Después de agitar durante 10 minutos, bromuro de metilmagnesio (17.00 ml, 3.00 M en éter, 51.00 mmol) se agrega por goteo. La solución se calienta lentamente a 60 °C y se agita durante 3 h a 60 °C, entonces durante la noche a temperatura ambiente. La mezcla de reacción naranja oscuro resultante se extingue con ácido clorhídrico 1 N y se ajusta a pH ~5, entonces se extrae con etil acetato y agua saturada con cloruro de sodio. La capa orgánica se lava con agua y salmuera, se seca sobre sulfato de magnesio, se filtra y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía de columna en gel de sílice eluyendo con acetato de etilo y hexano. Las fracciones apropiadas se combinan y se concentran bajo vacío para proporcionar el compuesto deseado como un sólido amarillo (**8**, 202 mg). ^{1}H-NMR(dmso-d6) es consistente con el compuesto deseado. MS(ESI) $[M+H^+]^+$ = 134.3.

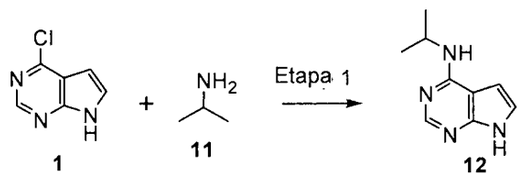
[0216] 4-Isopropil-7H-pirrolo[2,3-d]pirimidina **8**, 4-isobutil-7H-pirrolo[2,3-d]pirimidina **9**, y 4-ciclopropil-1H-pirrolo[2,3-b]piridina **10**,



se preparan al seguir el protocolo del Esquema 1a, reemplazando el bromuro de metilmagnesio con bromuro de isopropilmagnesio, bromuro de isobutilmagnesio, y bromuro de ciclopropilmagnesio, respectivamente. MS (ESI) $[M+H^+]^+$ = 162.1 (**8**); y 176.1 (**9**).

[0217] La isopropil-(7H-pirrolo[2,3-d]pirimidin-4-il)-amina **12** se sintetiza en una etapa a partir de 4-cloro-7H-pirrolo[2,3-d]pirimidina **1** como se muestra en el Esquema 1b.

Esquema 1b



Etapa 1 – Preparación de isopropil-(7H-pirrolo[2,3-d]pirimidin-4-il)-amina (12):

[0218] A 4-cloro-7H-pirrolo[2,3-d]pirimidina (**1**, 168 mg, 1.09 mmol), se agregan 2.00 ml de alcohol isopropílico, seguido por 2-propanamina (**11**, 0.280 ml, 3.28 mmol). La reacción se calienta por microondas a 120 °C durante 20 minutos, y luego por 40 minutos adicionales. Otros 0.250 ml de 2-propanamina se agregan y se calienta a 120 °C durante 60 minutos. La reacción se vierte en agua y se extrae con acetato de etilo. La capa orgánica se concentra bajo vacío y se purifica por cromatografía de columna en gel de sílice, eluyendo con un gradiente de 1-5% de metanol en diclorometano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (**12**, 172 mg). MS (ESI) $[M+H^+]^+ = 176.85$.

[0219] Compuestos adicionales se preparan al seguir el protocolo del Esquema 1b. En algunos casos, sin limitación, la *4-cloro*-7H-pirrolo[2,3-d]pirimidina **1** se hace reaccionar directamente en el compuesto amina líquido sin solvente adicional (por ejemplo, alcohol isopropílico). Los compuestos se preparan al sustituir la 2-propanamina **11** con una amina adecuada. *Los siguientes compuestos se elaboran utilizando este procedimiento.*

*Isobutil-(7H-pirrolo[2,3-d]pirimidin-4-il)-amine (**13**),*

(7H-Pirrolo[2,3-d]pirimidin-4-il)-(tetrahidro-piran-4-il)-amine *(**14**),*

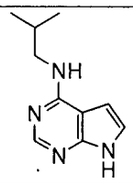
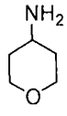
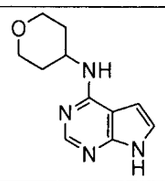
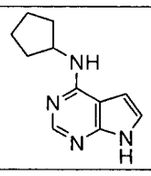
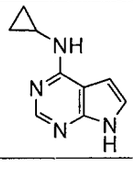
*Ciclopentil-(7H-pirrolo[2,3-d]pirimidin-4-il)-amine (**15**),*

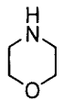
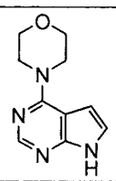
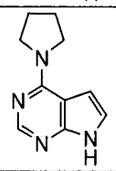
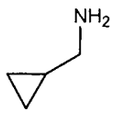
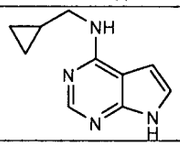
*Ciclopropil-(7H-pirrolo[2,3-d]pirimidin-4-il)-amine (**16**)*

*4-Morfolin-4-il-7H-pirrolo[2,3-d]pirimidine (**17**), and*

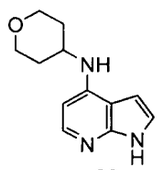
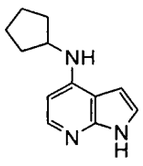
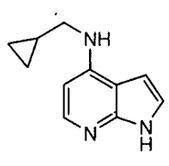
*4-Pirrolidin-1-il-7H-pirrolo[2,3-d]pirimidine (**18**).*

La siguiente tabla indica el compuesto amina (columna 2) utilizado para ofrecer el compuesto deseado (columna 3). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 4.

Número de compuesto	Amina	Estructura del compuesto	MS (ESI) $[M+H^+]^+$
13			191.1
14			219.1
15			203.0
16			175.1

17			205.0
18			189.0
19			189.0

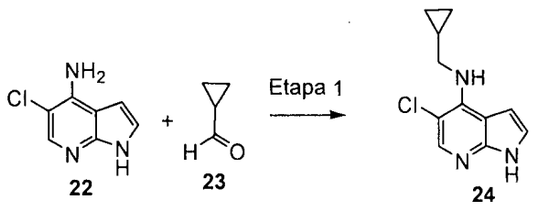
[0220] Compuestos 1H-pirrolo[2,3-b]piridina sustituidos de manera similar en la posición 4, (1H-pirrolo[2,3-b]piridin-4-il)-(tetrahidro-piran-4-il)-amina **20**, ciclopentil-(1H-pirrolo[2,3-b]piridin-4-il)-amina **21**, y ciclopropilmetil-(1H-pirrolo[2,3-b]piridin-4-il)-amina **21-A**,

 **20** ,  **21** , y  **21-A** ,

también se preparan al seguir el protocolo del Esquema 1b, sustituyendo la 2-propanamina **11** *con tetrahidro-piran-4-ilamina, ciclopentilamina, y c-ciclopropil-metilamina, respectivamente,* **y al utilizar 4-cloro-**1H-pirrolo[2,3-b]piridina en lugar de *4-cloro-*7H-pirrolo[2,3-d]pirimidina **1**. Estas reacciones se llevan a cabo al utilizar tolueno como solvente, e incluir Pd(OR)(OAc) y ter-butóxido de potasio en la reacción. Pd(OR)(OAc) es un catalizador de paladio en donde R es 2-(di-ter-butilfosfino)bifenilo, preparado al combinar acetato de paladio(II) (225 mg, 1 mmol) con 2-(di-ter-butilfosfino)bifenilo (299 mg, 1 mmol) en 15 ml de tolueno. La solución se agita durante la noche a temperatura ambiente para su uso en la reacción anterior. MS (ESI) $[M+H^+]^+ = 218.1$ (**20**), 202.4 (**21**), y 187.8 (**21-A**).

[0221] La (5-Cloro-1H-pirrolo[2,3-b]piridin-4-il)-ciclopropilmetil-amina 24 se sintetiza en una etapa a partir de 5-cloro-1H-pirrolo[2,3-b]piridin-4-ilamina 22 como se muestra en el Esquema 1c.

Esquema 1c



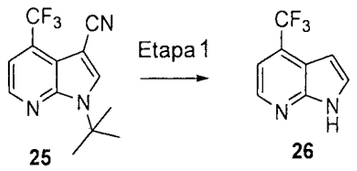
22 **23** **24**

*Etapa 1 – Preparación de (5-cloro-1H-pirrolo[2,3-b]piridin-4-il)-ciclopropilmetil-amina (**24**):*

[0222] En un matraz de fondo redondo, 5-cloro-1H-pirrolo[2,3-b]piridin-4-ilamina (**22**, 0.21 g, 1.25 mmol) se combina con 3.5 ml de etanol, ácido acético (0.38 g, 6.25 mmol), cianoborohidruro de sodio unido a sílice (1.1g, 1.02 mmol), y ciclopropanocarbaldehído (**23**, 0.26 g, 4 mmol). La mezcla de reacción se agitó durante la noche a temperatura ambiente, se calentó hasta 145 °C hasta que la reacción se completó, se filtró, concentró, y purificó por cromatografía instantánea para proporcionar el compuesto como un sólido (**24** , 0.191 g; rendimiento = 69%).

[0223] La 4-trifluorometil-1H-pirrolo[2,3-b]piridina **26** se sintetiza en una etapa a partir de *1-ter-butil-4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonitrilo* **25** como se muestra en el Esquema 1d.

Esquema 1d



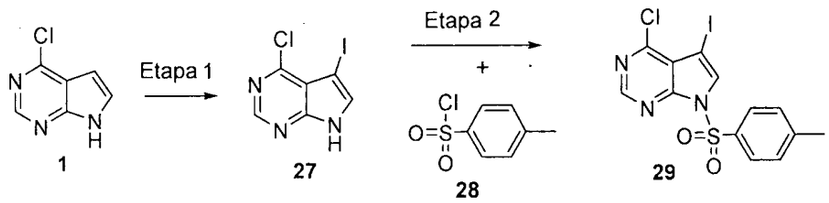
25 **26**

Etapa 1 – Preparación de 4-trifluorometil-1H-pirrolo[2,3-b]piridina (26):

[0224] El *1-ter-butil-4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonitrilo* (**25**, 1.071 g, 4.007 mmol) se disuelve en 10 ml de ácido sulfúrico acuoso al 60% y se agita a 120 °C durante 20 horas. La reacción se ajusta a pH ~7 con hidróxido de sodio y bicarbonato de sodio acuoso saturado, entonces se extrae con etil acetato. La capa orgánica se lava con agua, luego con salmuera, y se seca sobre sulfato de magnesio, se filtra y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía de columna en gel de sílice, eluyendo con etil acetato y hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (26, 373 mg). *MS (ESI) [M+H$^+$]$^+$ = 187.1.*

[0225] La 4-cloro-5-yodo-7-(tolueno-4-sulfonil)-7H-pirrolo[2,3-d]pirimidina 29 se sintetiza en dos etapas a partir de *4-cloro*-7H-pirrolo[2,3-d]pirimidina 1 como se muestra en el Esquema 1e.

Esquema 1e



1 **27** **28** **29**

Etapa 1 – Preparación de 4-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidina (27):

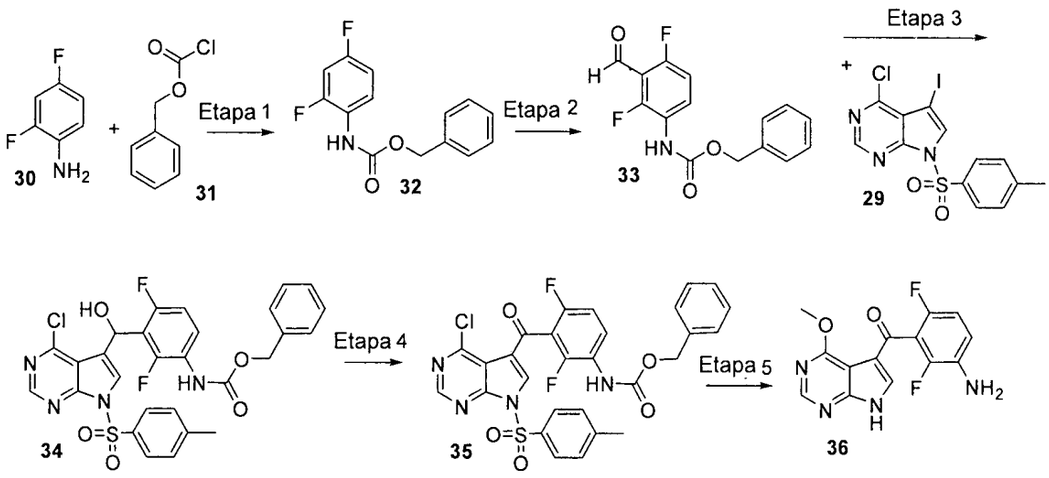
[0226] A 4-cloro-7H-pirrolo[2,3-d]pirimidina (**1**, 1.21 g, 7.88 mmol) disuelta en 50 ml de diclorometano, N-yodosuccinimida (1.95 g, 8.67 mmol) se agrega y la reacción se agita a temperatura ambiente durante la noche. La reacción se extingue con 50% de tiosulfato de sodio acuoso y la mezcla se filtra a través de celite. La capa acuosa se extrae con etil acetato. Las capas orgánicas se combinan y lavan con agua, luego con salmuera, y se secan con sulfato de sodio, se filtran y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía de columna en gel de sílice, eluyendo con etil acetato y diclorometano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (27, 1.383 g). MS (ESI) $[M+H^+]^+ = 279.8, 281.8$.

Etapa 2 – Preparación de 4-cloro-5-yodo-7-(tolueno-4-sulfonil)-7H-pirrolo[2,3-d]pirimidina (29):

[0227] A 4-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidina (27, 2.45 g, 8.77 mmol) en 68 ml de tetrahidrofurano, se agrega hidruro de sodium (0.4208 g, 10.52 mmol) y la reacción se agita a temperatura ambiente durante 30 minutos. Cloruro de 4-metilo-bencenosulfonilo (28, 1.838 g, 9.643 mmol) se agrega y la reacción se agita a temperatura ambiente durante la noche. Se agrega agua y la reacción se extrae con etil acetato, lo que resulta en cierto precipitado que se remueve por filtración. La capa acuosa se separa y extrae con etil acetato. Las capas orgánicas se combinan y lavan con agua, luego con salmuera, y se secan con sulfato de magnesio, se filtran y el filtrado se concentra bajo vacío. El residuo se suspende en etil acetato, se somete a sonicación durante 30 minutos, y el sólido se recolecta por filtración para proporcionar el compuesto deseado (29, 3.325 g). MS (ESI) $[M+H^+]^+ = 433.8$.

[0228] La (3-amino-2,6-difluoro-fenil)-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona 36 se sintetiza en cinco etapas a partir de 2,4-difluoroanilina 30 como se muestra en el Esquema 1f.

Esquema 1f



Etapa 1 - Preparación de bencil éster del ácido (2,4-difluoro-fenil)-carbámico (32):

[0229] A 2,4-difluoro-fenilamina (**30**, 7.0 ml, 70.0 mmol) en 100 ml de diclorometano, se agrega piridina (11 ml, 0.14 mol) y cloroformato de bencilo (**31**, 11.9 ml, 83.4 mmol). La mezcla de reacción se agita a temperatura ambiente durante 1.5 horas. La mezcla de reacción se concentra bajo vacío y el residuo se divide entre etil acetato y solución de disulfato de potasio. La capa orgánica se seca con sulfato de magnesio, se filtra, y el filtrado se concentra bajo vacío. El material resultante se cristaliza a partir de hexanos para proporcionar el compuesto deseado (**32**, 15.6 g, 85%).

Etapa 2 - Preparación de bencil éster del ácido (2,4-difluoro-3-formil-fenil)-carbámico (33):

[0230] En un matraz de fondo redondo el bencil éster del ácido (2,4-difluoro-fenil)-carbámico (**30**, 3.83 g, 14.5 mmol) se combina con 148 ml de tetrahidrofurano. La solución se enfría a -78 °C y n-butillitio (19.1 ml, 1.60 M en hexano, 30.0 mmol) se agrega durante 30 minutos, seguido por la adición de N,N-dimetilformamida (1.12 ml, 14.5 mol). La mezcla de reacción se deja calentar a temperatura ambiente y se agita durante la noche, entonces se vierte en agua y se extrae con etil acetato. La capa orgánica se lava con salmuera, se seca sobre sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. El material resultante se cristaliza a partir de éter para proporcionar el compuesto deseado (**33**, 3.0 g, 71%).

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Etap 3 - Preparación de bencil éster del ácido (3-{[4-cloro-7-(tolueno-4-sulfonil)-7H-pirrolo[2,3-d]pirimidin-5-il]-hidroxi-metil}-2,4-difluoro-fenil)-carbámico (34):

[0231] En un matraz de fondo redondo, la 4-cloro-5-yodo-7-(tolueno-4-sulfonil)-7H-pirrolo[2,3-d]pirimidina (**29**, 1.549 g, 3.572 mmol) se combina con 25.0 ml de tetrahidrofurano y la solución se enfría a -50 °C bajo nitrógeno. Cloruro de isopropilmagnesio (2.76 ml, 2.0 M en tetrahidrofurano, 5.00 mmol) se agrega lentamente y la reacción se deja calentar a 5 °C durante 70 minutos, entonces se enfría a -45 °C. En un recipiente separado, el bencil éster del ácido (2,4-difluoro-3-formil-fenil)-carbámico (**33**, 805 mg, 2.76 mmol) en 5 ml de tetrahidrofurano se enfría a -5 °C y cloruro de o-tolilmagnesio (2.76 ml, 1 M en tetrahidrofurano, 2.76 mmol) se agrega por goteo lentamente, menteniendo la temperatura a -5 °C para 1 hora. Este entonces se enfría a -30 °C y se agrega a la mezcla de reacción de 4-cloro-5-yodo-7-(tolueno-4-sulfonil)-7H-pirrolo[2,3-d]pirimidina. La mezcla de reacción resultante se calienta a temperatura ambiente durante 2-3 horas, entonces se extingue con la adición de ácido cítrico acuoso 1 M y se extrae con etil acetato. La capa orgánica se lava con agua, salmuera, y se seca sobre sulfato de magnesio, entonces se filtra y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía de columna en gel de sílice eluyendo con acetato de etilo y hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (**34**, 445 mg). MS(ESI) $[M+H^+]^+ = 598.8$.

Etapa 4 – Preparación de bencil éster del ácido {3-[4-cloro-7-(tolueno-4-sulfonil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-carbámico (35):

[0232] En un matraz de fondo redondo, el bencil éster del ácido (3-{[4-cloro-7-(tolueno-4-sulfonil)-7H-pirrolo[2,3-d]pirimidin-5-il]-hidroxi-metil}-2,4-difluoro-fenil)-carbámico (34, 311 mg, 0.519 mmol) se disuelve en 35 ml de tetrahidrofurano y se agrega periodinano de Dess-Martin (242 mg, 0.571 mmol). La mezcla resultante se agita a temperatura ambiente, y se agrega periodinano de Dess-Martin adicional. Después de 60 minutos, la reacción se extingue con agua y se extrae con etil acetato. La capa orgánica se lava con bicarbonato de sodio acuoso, luego salmuera, y se seca con sulfato de magnesio, se filtra y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía en gel de sílice eluyendo con acetato de etilo y hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (**35**, 152 mg). MS(ESI) $[M+H^+]^+ = 596.8$.

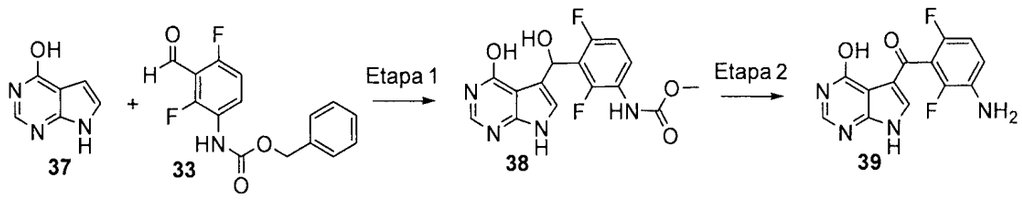
Etapa 5 – Preparación de (3-amino-2,6-difluoro-fenil)-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (36):

[0233] El bencil éster del ácido {3-[4-cloro-7-(tolueno-4-sulfonilo)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-carbámico (35, 152 mg, 0.255 mmol) se combina con 15 ml de metanol e hidróxido de potasio (1.06 g, 18.9 mmol) se agrega. La mezcla se calienta a 70 °C durante 36 horas, entonces ácido clorhídrico acuoso 6 N se agrega y la mezcla se extrae con etil acetato. La capa orgánica se lava con salmuera, entonces seca con sulfato de magnesio, se filtra y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía de columna en gel de sílice, eluyendo con etil acetato y hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (**36**, 0.03 mg). MS(ESI) $[M+H]^+ = 305.1$.

[0234] La (3-amino-2,6-difluoro-fenil)-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona 39 se

sintetiza en dos etapas a partir de 7H-pirrolo[2,3-d]pirimidin-4-ol 37 y el bencil éster del ácido (2,4-difluoro-3-formil-fenil)-carbámico 33 como se muestra en el Esquema 1g.

Esquema 1g



Etapa 1 – Preparación del metil éster del ácido {2,4-difluoro-3-[hidroxi-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-il)-metil]-fenil}-carbámico (38):

[0235] En un recipiente de reacción, 7H-pirrolo[2,3-d]pirimidin-4-ol (**37**, 855 mg, 6.33 mmol) se combina con el bencil éster del ácido (2,4-difluoro-3-formil-fenil)-carbámico (**33**, 2.03 g, 6.96 mmol) e hidróxido de potasio (1.06 g, 19.0 mmol) y se agregan 5 ml de metanol. La solución resultante se agita a 50 °C durante 2 días. La reacción se diluye con ácido clorhídrico 1 N y se extrae con etil acetato, y los sólidos resultantes se recolectan por filtración y se secan bajo vacío. La capa orgánica se separa del filtrado y la capa acuosa se extrae dos veces más con etil acetato. Las capas orgánicas se combinan y lavan con agua, salmuera, se secan con sulfato de magnesio y se filtran. El filtrado se concentra bajo vacío y el material resultante se suspende en acetonitrilo y se somete a sonicación durante 1 hora. El sólido se recolecta por filtración y se seca bajo vacío, entonces se combina con el primer sólido recolectado para proporcionar el compuesto deseado (**38**, 2.05 g). MS(ESI) $[M-H^+]^-$ = 349.0.

Etapa 2 – Preparación de (3-amino-2,6-difluoro-fenil)-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (39):

[0236] En un recipiente de reacción, el metil éster del ácido {2,4-difluoro-3-[hidroxi-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-il)-metil]-fenil}-carbámico (38, 690 mg, 1.97 mmol) se disuelve en 200 ml de tetrahidrofurano y se agrega periodinano de Dess-Martin (877.3 mg, 2.068 mmol). La mezcla resultante se agita a temperatura ambiente durante 3 horas, entonces 20 ml de bicarbonato de sodio saturado acuoso, 5 ml de tiosulfato de sodio saturado acuoso, y 100 ml de etil acetato se agregan para extracción. La capa orgánica se aísla y la capa acuosa se extrae con 50 ml de etil acetato. Las fracciones orgánicas se combinan y lavan con agua, luego con salmuera, y se secan con sulfato de magnesio, se filtran y el filtrado se concentra bajo vacío. El material resultante se suspende en acetonitrilo, se somete a sonicación durante 1 hora, entonces se filtra para recolectar el material sólido, el cual entonces se lava con acetonitrilo. El material resultante se suspende en 15 ml de dioxano, y se combina con 15 ml de hidróxido de sodio acuoso 10 N, y se calienta a reflujo durante 5 horas. La mezcla de reacción se ajusta a pH aproximadamente 6 con ácido clorhídrico 6 N y se extrae con etil acetato. La capa orgánica se concentra bajo vacío y el material resultante se purifica por cromatografía en gel de sílice eluyendo con metanol y diclorometano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (**39**, 287 mg). MS(ESI) $[M-H^+]^-$ = 289.1.

[0237] Compuestos adicionales se preparan al seguir el protocolo del Esquema 1f o 1g, al hacer reaccionar una 7H-pirrolo[2,3-d]pirimidina o 1H-pirrolo[2,3-b]piridina adecuada con el aldehído 33 (o

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alternativamente con el metil éster del ácido (2,4-difluoro-3-formil-fenil)-carbámico). *Los siguientes compuestos se elaboran usando este procedimiento.*

(3-Amino-2,6-difluoro-fenil)-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-il)-methanone ***(40)***,

(3-amino-2,6-difluoro-fenil)-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-il)-methanone (41),

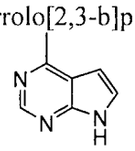
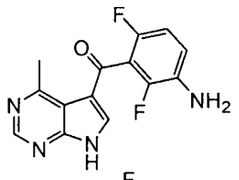
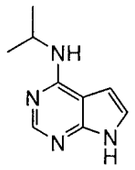
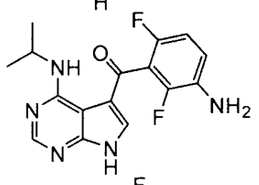
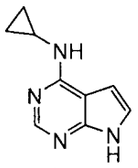
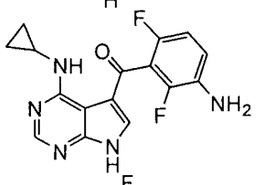
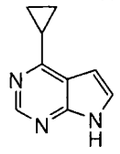
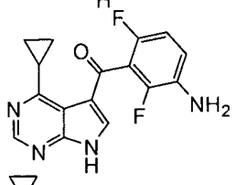
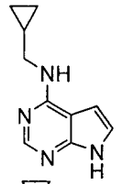
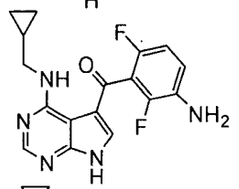
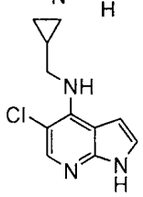
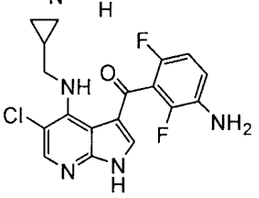
(3-Amino-2,6-difluoro-fenil)-(4-ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-il)-methanone (42),

(3-Amino-2,6-difluoro-fenil)-(4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-methanone (43),

(3-Amino-2,6-difluoro-fenil)-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-il]-methanone (44), *and*

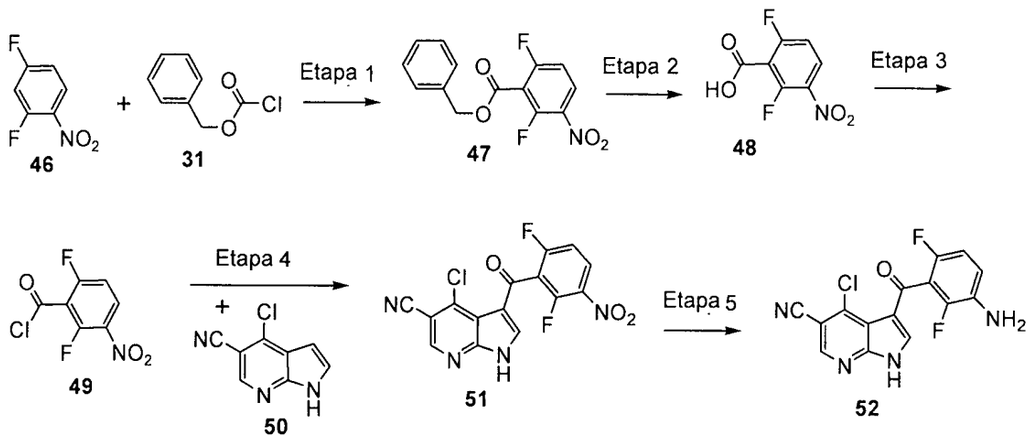
*(3-Amino-2,6-difluoro-fenil)-[5-cloro-4-(ciclopropilmetil-amino)-1H-pirrolo[2,3-b]piridin-3-il]-methanone (**45**).*

La siguiente tabla indica el compuesto 7H-pirrolo[2,3-d]pirimidina o 1H-pirrolo[2,3-b]piridina (columna 2) utilizado para ofrecer el compuesto deseado (columna 3). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 4.

Número de compuesto	7H-pirrolo[2,3-d]pirimidina o 1H-pirrolo[2,3-b]piridina	Estructura del compuesto	MS (ESI) $[M+H^+]^+$
40			
41			331.9
42			329.9
43			314.9
44			343.9
45			

[0238] El 3-(3-amino-2,6-difluoro-benzoil)-4-cloro-1H-pirrolo[2,3-b]piridin-5-carbonitrilo 52 se sintetiza en cinco etapas a partir de 2,4-difluoro-1-nitro-benceno 46 y cloroformato de bencilo 31 como se muestra en el Esquema 1h.

Esquema 1h



Etapa 1 – Preparación de bencil éster del ácido 2,6-difluoro-3-nitro-benzoico (47):

[0239] 2,4-Difluoro-1-nitro-benceno (**46**, 1.4 ml, 13.0 mmol) y cloroformato de bencilo (**31**, 10.42 g, 61.1 mmol) en 20 ml de tetrahidrofurano se enfría a -78 °C y se agita durante 1 hora. Diisopropilamina de litio (1.5 g, 14.0 mmol) se agrega por goteo y la reacción se agita a -78 °C durante 1 hora, entonces se calienta a temperatura ambiente durante 2 horas. La reacción se purificó por cromatografía en gel de sílice, eluyendo con hexano:etil acetato 90:10. Fracciones apropiadas se combinan y concentran bajo vacío, entonces are lavado con metanol y el sólido recolectado por filtración para proporcionar el compuesto deseado (**47**, 110 mg).

Etapa 2 – Preparación de ácido 2,6-difluoro-3-nitro-benzoico (48):

[0240] Al bencil éster del ácido 2,6-difluoro-3-nitro-benzoico (**47**, 750 mg, 2.6 mmol) en 4 ml de tetrahidrofurano y 2 ml de agua, hidróxido de sodio (0.2 g, 5.0 mmol) se agrega y la reacción se agita durante 2 horas. La reacción se acidifica con ácido clorhídrico diluido y se extrae con etil acetato. La capa orgánica se concentra bajo vacío para proporcionar el compuesto deseado (**48**, 300 mg).

Etapa 3 – Preparación de cloruro de 2,6-difluoro-3-nitro-benzoilo (49):

[0241] A ácido 2,6-difluoro-3-nitro-benzoico (**48**, 5.50 g, 27.1 mmol), cloruro de tionilo (20 ml, 300 mmol) se agrega seguido por N,N-dimetilformamida (0.1 ml, 2.0 mmol) y la reacción se calienta en un baño de aceite a 80 °C. Después de la reacción durante la noche, la mezcla de reacción se concentra bajo vacío, se somete a azeótropos con tolueno (2X) para proporcionar el compuesto deseado (**49**, 5.95 g).

Etapa 4 – Preparación de 4-cloro-3-(2,6-difluoro-3-nitro-benzoil)-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (51):

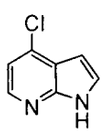
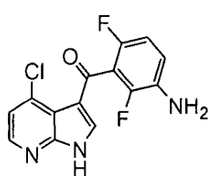
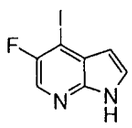
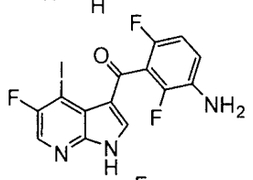
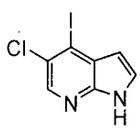
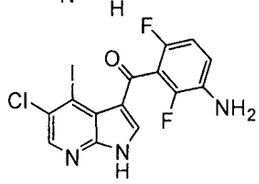
[0242] En un vial, 4-cloro-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**50**, 500 mg, 2.82 mmol) se enfría en un baño de agua helada, y se agrega ácido trifluorometanosulfónico (2.49 ml, 28.15 mmol). La solución se agita a 0-5 °C durante 5 minutos, entonces se agrega cloruro de 2,6-difluoro-3-nitro-benzoilo (**49**, 748.5 mg, 3.38 mmol). La reacción se agita a 0-5 °C durante 1 hora, entonces se calienta a temperatura ambiente y se agita durante 4 días. La reacción se extingue con 5 ml de metanol, y se agita a temperatura ambiente durante 1 hora. La reacción se vierte en bicarbonato de sodio saturado acuoso y se extrae con etil acetato. La capa orgánica se lava con agua, salmuera, se seca con sulfato de magnesio, se filtra y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía de columna en gel de sílice eluyendo con 0-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinan y

concentran bajo vacío para proporcionar el compuesto deseado (**51**, 134 mg).

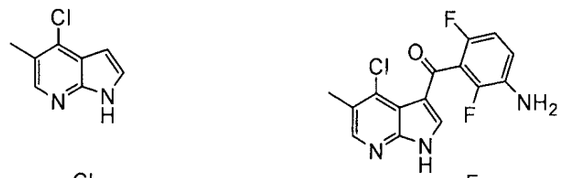
*Etapa 5 – Preparación de 3-(3-amino-2,6-difluoro-benzoilo)-4-cloro-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(52)**:*

[0243] En un matraz de fondo redondo, 4-cloro-3-(2,6-difluoro-3-nitro-benzoil)-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**51**, 0.15 g, 0.42 mmol) en 10 ml de etanol y 10 ml de tetrahidrofurano, se agrega cloruro de estaño(II) (0.1 ml, 2.1 mmol). Se agregan 10 ml adicionales de tetrahidrofurano para dar una solución transparente, y la reacción se calienta a 60 °C durante 24 horas. La reacción se combina con 10 ml de agua y 10 ml de bicarbonato de sodio saturado acuoso y se agregan 20 ml de etil acetato. Se agrega celite con mezclado, y entonces se filtra. Se agrega salmuera al filtrado y las capas se separan. La capa orgánica se lava con agua, salmuera, se seca con sulfato de magnesio, se filtra y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía de columna en gel de sílice, eluyendo con 0-80% de acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (**52**, 123 mg). MS (ESI) $[M+H^+]^+$ = 332.8 y 334.8.

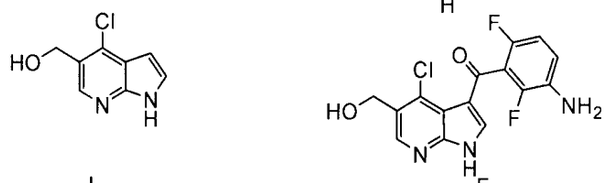
[0244] Compuestos adicionales sustituidos de (3-amino-2,6-difluoro-fenil)-(1H-pirrolo[2,3-b]piridin-3-il)-metanona se preparan al seguir el protocolo del Esquema 1h. Los compuestos se preparan al sustituir el 4-cloro-1H-pirrolo[2,3-b]piridin-5-carbonitrilo 50 con una 1H-pirrolo[2,3-b]piridina sustituida adecuada en la etapa 4. *Los siguientes compuestos se elaboran usando este procedimiento.*
(3-Amino-2,6-difluoro-fenil)-(4-cloro-1H-pirrolo[2,3-b]piridin-3-il)-methanone ***(53)***,
(3-Amino-2,6-difluoro-fenil)-(5-fluoro-4-iodo-1H-pirrolo[2,3-b]piridin-3-il)-methanone (54),
*(3-Amino-2,6-difluoro-fenil)-(5-cloro-4-iodo-1H-pirrolo[2,3-b]piridin-3-il)-methanone **(55)**,*
*(3-Amino-2,6-difluoro-fenil)-(4-cloro-5-metil-1H-pirrolo[2,3-b]piridin-3-il)-methanone **(56)**,*
*(3-Amino-2,6-difluoro-fenil)-(4-cloro-5-hidroximetil-1H-pirrolo[2,3-b]piridin-3-il)-methanone **(57)**, and*
*(3-Amino-2,6-difluoro-fenil)-(4-iodo-5-metoxi-1H-pirrolo[2,3-b]piridin-3-il)-methanone **(58)**.*
La siguiente tabla indica el compuesto de 1H-pirrolo[2,3-b]piridina (columna 2) utilizado en la etapa 4 para ofrecer el compuesto deseado (columna 3). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 4.

Número de compuesto	1H-pirrolo[2,3-b]piridina	Estructura del compuesto	MS (ESI) $[M-H^+]^-$
53			308.3
54			418.0
55			

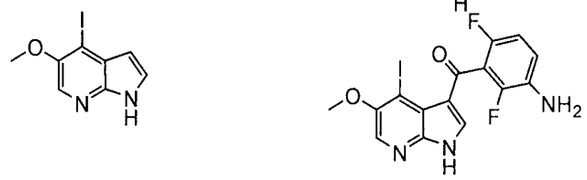
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57



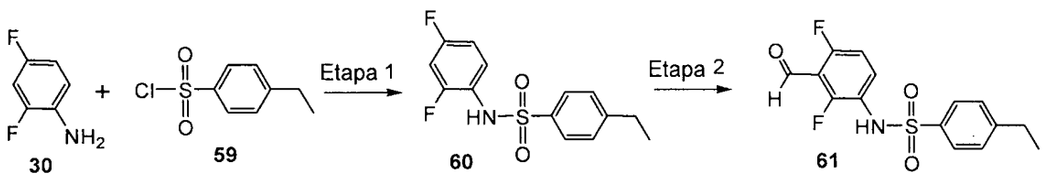
58



Ejemplo 2: Síntesis de N-(2,4-difluoro-3-formil-fenil)-4-etil-bencenosulfonamida **61**.

[0245] La N-(2,4-difluoro-3-formil-fenil)-4-etil-bencenosulfonamida **61** se sintetiza en dos etapas a partir de 2,4-difluoro-fenilamina **30** y cloruro de 4-etil-bencenosulfonilo **59** como se muestra en el Esquema 2.

Esquema 2



Etapa 1– Preparación de N-(2,4-difluoro-fenil)-4-etil-bencenosulfonamida (60):

[0246] A 2,4-difluoro-fenilamina (**30**, 2.0 g, 15.5 mmol) en 20 ml de diclorometano, se agrega piridina (1.326 ml, 16.4 mmol) y dimetilaminopiridina (0.076 g, 0.62 mmol) seguido por la adición por goteo de cloruro de 4-etil-bencenosulfonilo (**59**, 3.357 g, 16.4 mmol) y la reacción se calienta a reflujo durante la noche. La reacción se concentra bajo vacío a sequedad, entonces se recoge en etil acetato y agua para extracción. La capa orgánica se aísla y se concentra bajo vacío. El material resultante se purifica por cromatografía de columna en gel de sílice, eluyendo con un gradiente de 10-20% de acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (**60**, 4.344 g).

Etapa 2– Preparación de N-(2,4-difluoro-3-formil-fenil)-4-etil-bencenosulfonamida (61):

[0247] A N,N-diisopropilamina (4.50 ml, 32.1 mmol) en 130 ml de tetrahidrofurano, n-butilitio (12.8 ml, 2.50 M en hexano, 32.1 mmol) se agrega a -78 °C bajo nitrógeno. Después de 15 minutos, N-(2,4-difluoro-fenil)-4-etil-bencenosulfonamida (60, 4.344 g, 14.61 mmol) en 20 ml de tetrahidrofurano se agrega a -78 °C bajo nitrógeno. Después de 30 minutos, N,N-dimetilformamida (2.83 ml, 36.5 mmol) se agrega y la reacción continúa a -78 °C bajo nitrógeno durante 1 hora, entonces se calienta a temperatura ambiente durante 60 minutos. La reacción se extingue con 6 ml de ácido clorhídrico acuoso 6 N. La capa acuosa se extrae con etil acetato. Las capas orgánicas se

combinan y lavan con salmuera, se secan sobre sulfato de magnesio, se filtran y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía de columna en gel de sílice, eluyendo con un gradiente de 5-35% de acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (61, 2.634 g). MS (ESI) $[M-H^+]^-$ = 324.2.

[0248] Compuestos adicionales de aldehído se preparan al seguir el protocolo del Esquema 2. Los compuestos se preparan al sustituir el cloruro de 4-etilo-bencenosulfonilo 59 con un cloruro de sulfonilo adecuado en la etapa 1. *Los siguientes compuestos se elaboran usando este procedimiento.*

*ácido 2-Metil-propano-1-sulfónico (2,4-difluoro-3-formil-fenil)-amida (**62**),*

N-(2,4-Difluoro-3-formil-fenil)-4-trifluorometil-bencenosulfonamida *(**63**),*

*N-(2,4-Difluoro-3-formil-fenil)-4-propil-bencenosulfonamida (**64**),*

*N-(2,4-Difluoro-3-formil-fenil)-4-isopropil-bencenosulfonamida (**65**),*

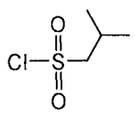
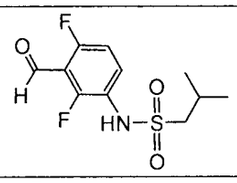
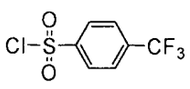
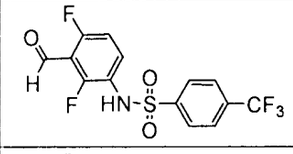
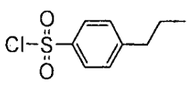
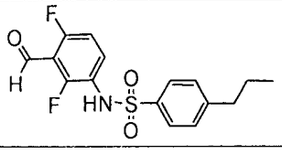
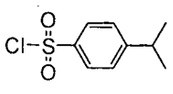
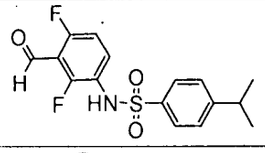
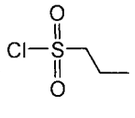
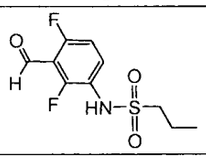
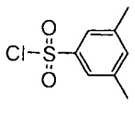
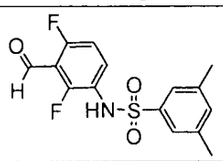
*Ácido propano-1-sulfónico (2,4-difluoro-3-formil-fenil)-amida (**66**),*

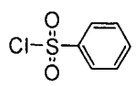
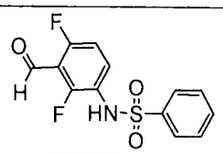
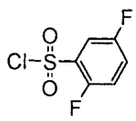
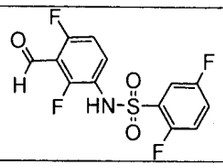
*N-(2,4-Difluoro-3-formil-fenil)-3,5-dimetil-bencenosulfonamida (**67**),*

*N-(2,4-Difluoro-3-formil-fenil)-bencenosulfonamida (**68**), and*

*N-(2,4-Difluoro-3-formil-fenil)-2,5-difluoro-bencenosulfonamida (**69**).*

La siguiente tabla indica el compuesto de cloruro de sulfonilo (columna 2) utilizado en la etapa 1 para ofrecer el compuesto aldehído deseado (columna 3). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 4.

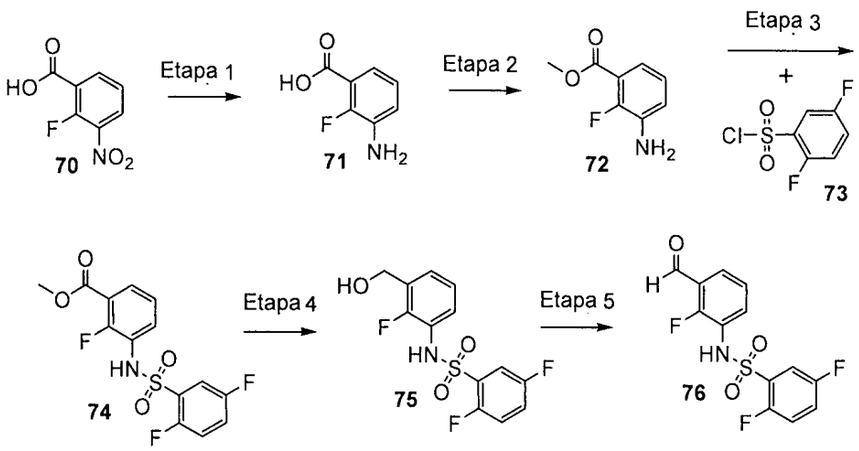
Número de compuesto	Cloruro de sulfonilo	Estructura de aldehído	MS (ESI) $[M-H^+]^-$
62			276.1
63			364.1
64			338.18
65			338.2
66			262
67			323.9

68			
69			331.9

Ejemplo 3: Síntesis de 2,5-difluoro-N-(2-fluoro-3-formil-fenil)-bencenosulfonamida **76.**

[0249] La 2,5-difluoro-N-(2-fluoro-3-formil-fenil)-bencenosulfonamida **76** se prepara en cinco etapas a partir de ácido 2-fluoro-3-nitro-benzoico **70** como se muestra en el Esquema 3.

Esquema 3



Etapa 1– Preparación de ácido 3-amino-2-fluoro-benzoico (71):

[0250] A ácido 2-fluoro-3-nitro-benzoico (**70**, 6.77 g, 36.6 mmol) en 150 ml de metanol, Paladio sobre carbono (5:95 Paladio:Carbono, 0.338 g, 0.159 mmol) se agrega bajo un globo de hidrógeno. La reacción se agita a temperatura ambiente durante 40 horas, entonces un nuevo globo de hidrógeno se une, y la reacción continúa durante 5 horas. La reacción se filtra y el filtrado se concentra bajo vacío para proporcionar el compuesto deseado (**71**, 5.62 g). MS (ESI) $[M\text{-}H^+]^-$ = 154.1.

Etapa 2– Preparación de metil éster del ácido 3-amino-2-fluoro-benzoico (72):

[0251] En un matraz de fondo redondo, ácido 3-amino-2-fluoro-benzoico (**71**, 2.51 g, 16.2 mmol) se disuelve en 100 ml de metanol y se agrega 1 ml de ácido sulfúrico concentrado. La reacción se calienta a reflujo durante 24 horas y 1 ml adicional de ácido sulfúrico concentrado se agrega. La reacción se calienta a reflujo por otras 20 horas, entonces se extrae con etil acetato y cloruro de sodio saturado acuoso. La capa orgánica se aísla y lava con agua, bicarbonato de sodio, y salmuera, entonces se seca con sulfato de magnesio, y se filtra. El filtrado se concentra bajo vacío para proporcionar el compuesto deseado (**72**, 2.688 g).

Etapa 3– Preparación de metil éster del ácido 3-(2,5-difluoro-bencenosulfonilamino)-2-fluoro-benzoico (74):

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[0252] Al metil éster del ácido 3-amino-2-fluoro-benzoico (**72**, 1.08 g, 6.4 mmol) en 40.64 ml de diclorometano, se agrega piridina (1.29 ml, 16 mmol), seguido por cloruro de 2,5-difluorobencenosulfonilo (**73**, 3.391 g, 16 mmol). La reacción se agita a temperatura ambiente durante la noche, entonces se extingue con ácido clorhídrico acuoso 1 M. La capa orgánica se remueve y la capa acuosa se extrae con diclorometano. Las capas orgánicas se combinan y se lavan con salmuera, entonces se secan sobre sulfato de sodio, se filtran y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía de columna en gel de sílice, eluyendo con etil acetato y hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (**74**, 0.956 g). MS (ESI) $[M-H^+]^-$ = 344.

*Etapa 4– Preparación de 2,5-difluoro-N-(2-fluoro-3-hidroximetil-fenil)-bencenosulfonamida (**75**):*

[0253] Al metil éster del ácido 3-(2,5-difluoro-bencenosulfonilamino)-2-fluoro-benzoico (**74**, 0.955 g, 2.8 mmol) en 22 ml de tetrahidrofurano, tetrahidroaluminato de litio (6 ml, 1 M en tetrahidrofurano, 6 mmol) se agrega a -40 °C bajo nitrógeno. La reacción se deja calentar a temperatura ambiente y se agita durante la noche. La reacción se vierte en hidróxido de sodio acuoso 1 M, entonces se neutraliza con ácido clorhídrico acuoso 1 M. Los sólidos se filtran a través de un lecho de celite, y el lecho de celite se lava con acetato de etilo y tetrahidrofurano. Las capas de filtrado se separan y la capa acuosa se extrae con acetato de etilo. Las capas orgánicas se combinan y se lavan con salmuera, se secan sobre sulfato de sodio, se filtran y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía de columna en gel de sílice, eluyendo con etil acetato y diclorometano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (**75**, 0.875 g). MS (ESI) $[M-H^+]^-$ = 316.

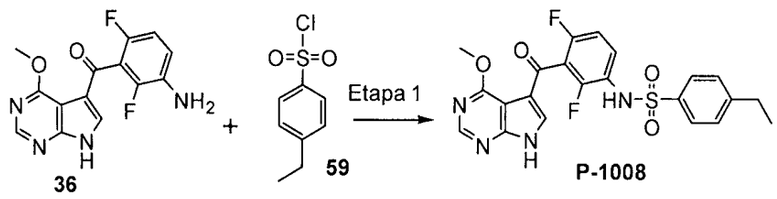
*Etapa 5– Preparación de 2,5-difluoro-N-(2-fluoro-3-formil-fenil)-bencenosulfonamida (**76**):*

[0254] 2,5-Difluoro-N-(2-fluoro-3-hidroximetil-fenil)-bencenosulfonamida (**75**, 950 mg, 2.99 mmol) y ácido 2-yodoxibenzoico estabilizado (2.608 g, 45%, 4.2 mmol) se disuelven en 150 ml de tetrahidrofurano y la reacción se agita a temperatura ambiente durante 16 horas. La reacción se vierte en agua y se extrae con acetato de etilo. La capa orgánica se lava con salmuera, se seca sobre sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía de columna en gel de sílice, eluyendo con etil acetato y diclorometano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (**76**, 0.944 g). MS (ESI) $[M-H^+]^-$ = 314.

Ejemplo 4: Síntesis de N-[2,4-difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida **P-1008**.

[0255] La N-[2,4-difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida **P-1008** se prepara en una etapa a partir de (3-amino-2,6-difluoro-fenil)-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona **36** y cloruro de 4-etil-bencenosulfonilo **59** como se muestra en el Esquema 4.

Esquema 4



*Etapa 1 - Preparación de N-[2,4-difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida (**P-1008**).*

[0256] A (3-amino-2,6-difluoro-fenil)-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (**36**, 30.0 mg, 0.0986 mmol) 1.0 ml de tetrahidrofurano y piridina (23.9 µL, 0.296 mmol) se agregan, seguido por cloruro de 4-etil-bencenosulfonilo (**59**, 40.4 mg, 0.197 mmol). El vial de reacción se agita a temperatura ambiente durante 5 días, entonces se extrae al agregar cloruro de sodio acuoso saturado y acetato de etilo. La capa orgánica se lava con agua, luego con bicarbonato de sodio, luego con salmuera, y se seca sobre sulfato de magnesio, se filtra y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía de columna en gel de sílice eluyendo con acetato de etilo y hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (**P-1008**, 27 mg). MS (ESI) $[M+H^+]^+ = 473.0$.

[0257] Compuestos adicionales se preparan al seguir el protocolo del Esquema 4, al reemplazar opcionalmente (3-amino-2,6-difluoro-fenil)-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona **36** con una (3-amino-2,6-difluoro-fenil)-(7H-pirrolo[2,3-d]pirimidin-5-il)-metanona apropiadamente 4-sustituida o (3-amino-2,6-difluoro-fenil)-(1H-pirrolo[2,3-b]piridin-3-il)-metanona adecuadamente sustituida y reemplazar opcionalmente el cloruro de 4-etil-bencenosulfonilo **59** con un cloruro de sulfonilo apropiado. *Los siguientes compuestos se elaboran usando este procedimiento.*

*N-[3-(4-Cloro-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (***77**),

ácido 6-Metoxi-piridin-3-sulfónico [2,4-difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1018**),

N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-fluoro-4-metoxi-bencenosulfonamida (**P-1036**),

N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1070**),

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (**P-1073**),

N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1104**),

N-[3-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-1107**),

4-Ciano-N-[2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-bencenosulfonamida (**P-1108**),

ácido 2,2,2-trifluoro-etanosulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1109**),

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-difluorometoxi-bencenosulfonamida (**P-1110**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1111**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,6-difluoro-bencenosulfonamida (**P-1112**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,4-difluoro-bencenosulfonamida (**P-1113**),
Ácido propano-2-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1114**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-fluoro-bencenosulfonamida (**P-1115**),
3-Ciano-N-[2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-bencenosulfonamida (**P-1116**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-fluoro-4-metoxi-bencenosulfonamida (**P-1117**),
ácido 3,3,3-Trifluoro-propano-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1118**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-difluorometoxi-bencenosulfonamida (**P-1119**),
ácido 1-Etil-1H-pirazol-4-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1120**),
ácido 1-Metil-1H-pirazol-4-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1121**),
Ácido Piperidin-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1122**),
Ácido ciclohexanosulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1123**),
Ácido ciclopentanosulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1124**),
Ácido pirrolidin-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1125**),
ácido 2-Metil-propano-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1126**),
Ácido dietilamin-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1127**),
Ácido ciclobutanosulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1128**),
Ácido morfolin-4-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1129**),
ácido 6-Metoxi-piridin-3-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-

carbonil)-fenil]-amida (**P-1130**),
ácido 6-metil-piridin-2-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1131**),
Ácido piridin-3-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1132**),
Ácido piridin-2-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1133**),
N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-bencenosulfonamida (**P-1155**),
Ácido dimetilamin-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (**P-1156**),
N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-1183**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,4-difluoro-bencenosulfonamida (**P-1186**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-bencenosulfonamida (**P-1187**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-4-metoxi-bencenosulfonamida (**P-1188**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-fluoro-bencenosulfonamida (**P-1189**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-4-metil-bencenosulfonamida (**P-1190**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3,5-difluoro-bencenosulfonamida (**P-1191**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-fluoro-2-metil-bencenosulfonamida (**P-1192**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-5-metil-bencenosulfonamida (**P-1193**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-5-trifluorometil-bencenosulfonamida (**P-1194**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-4-metil-bencenosulfonamida (**P-1195**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-4-metoxi-bencenosulfonamida (**P-1196**),
5-Cloro-N-{3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1197**),
3-Cloro-N-{3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida (**P-1198**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3,4-difluoro-bencenosulfonamida (**P-1199**),

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N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-5-trifluorometil-bencenosulfonamida (**P-1200**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-2-metil-bencenosulfonamida (**P-1201**),
4-Cloro-N-{3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-fluoro-bencenosulfonamida (**P-1202**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-5-fluoro-2-metil-bencenosulfonamida (**P-1203**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-5-fluoro-2-metoxi-bencenosulfonamida (**P-1204**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-3-trifluorometil-bencenosulfonamida (**P-1205**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,6-difluoro-bencenosulfonamida (**P-1206**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-bencenosulfonamida (**P-1207**),
Ácido piridin-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1208**),
ácido 4-Metil-piridin-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1209**),
ácido 6-Fluoro-piridin-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1210**),
Ácido piridin-3-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1211**),
ácido 4-Cloro-piridin-3-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1212**),
ácido 2-Cloro-piridin-3-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1213**),
ácido 1-Metil-1H-pirazol-4-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1214**),
Ácido N,N-Dimetilamino-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1215**),
Ácido N,N-Dietilamino-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1216**),
Ácido pirrolidin-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1217**),
Ácido morfolin-4-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1218**),
Ácido tetrahidro-piran-4-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1219**),
Ácido etanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-

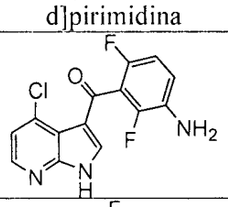
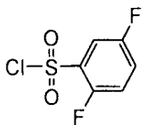
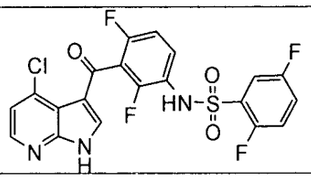
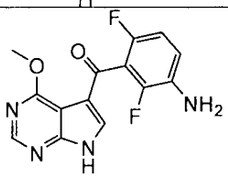
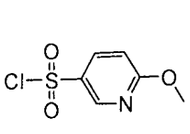
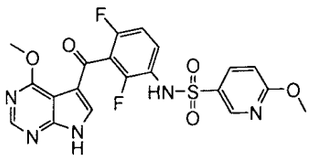
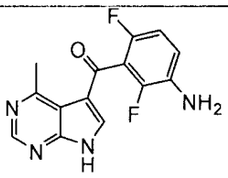
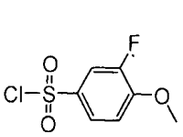
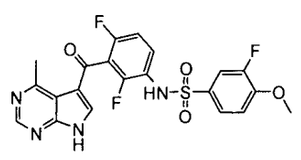
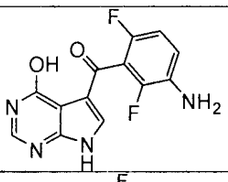
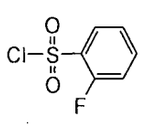
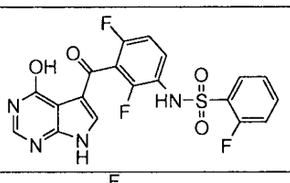
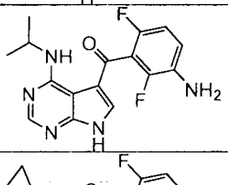
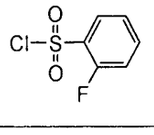
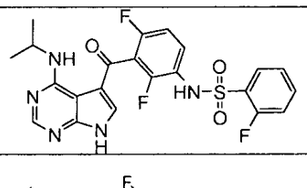
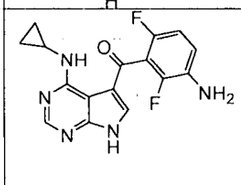
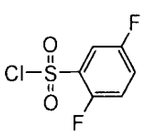
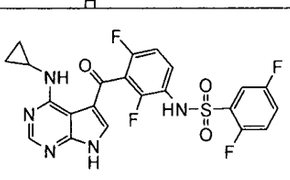
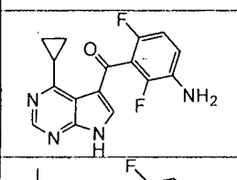
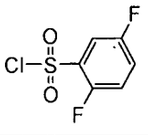
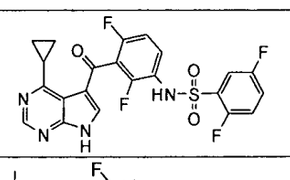
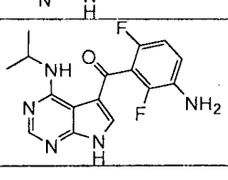
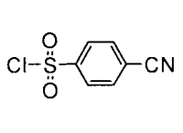
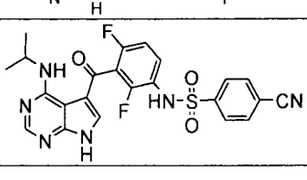
fenil}-amida (**P-1220**),
Ácido propano-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1221**),
Ácido butano-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1222**),
ácido 2-Metil-propano-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1223**),
Ácido Butano-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1224**),
Ácido Pentano-2-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1225**),
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-C,C,C-trifluoro-metanosulfonamida (**P-1226**),
ácido 2,2,2-trifluoro-etanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1227**),
ácido 3,3,3-Trifluoro-propano-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1228**),
Ácido ciclohexanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1229**),
Ácido ciclopentanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1230**),
Ácido ciclobutanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1231**),
Ácido ciclopropanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1232**),
ácido 4,4-Difluoro-ciclohexanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1233**),
3,3-Difluoro-ácido ciclopentanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1234**),
3-Fluoro-ácido ciclopentanosulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida (**P-1235**),
N-{3-[5-Cloro-4-(ciclopropilmetil-amino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida (**P-2021**),
N-[2,4-Difluoro-3-(5-fluoro-4-iodo-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-2025**),
N-[3-(4-Cloro-5-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-2026**)
N-[3-(5-Cloro-4-iodo-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-2027**),
N-[3-(4-Cloro-5-metil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-2028**),

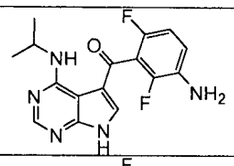
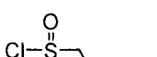
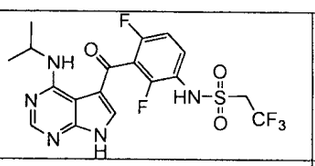
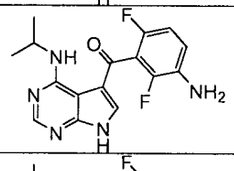
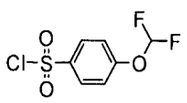
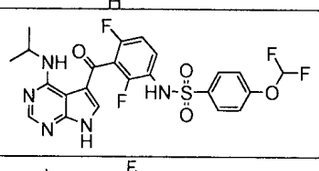
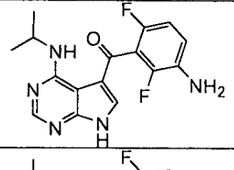
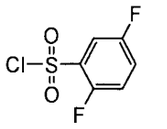
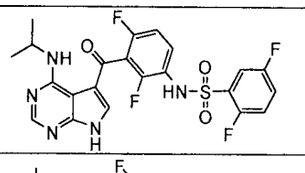
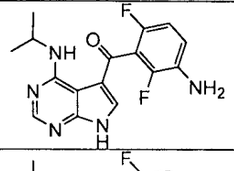
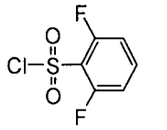
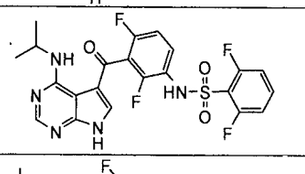
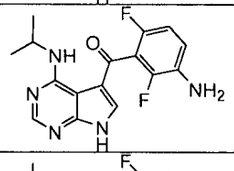
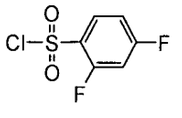
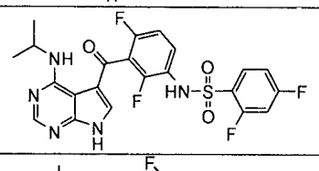
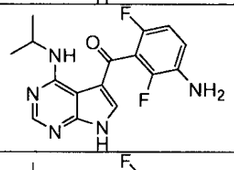
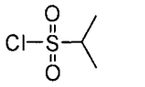
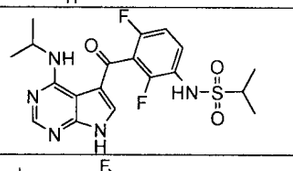
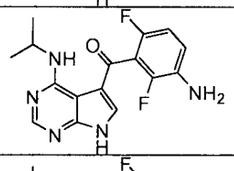
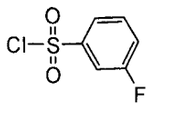
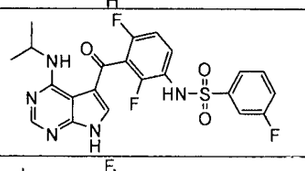
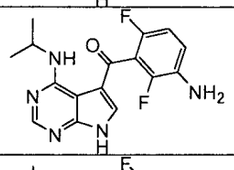
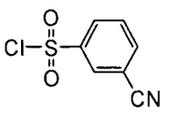
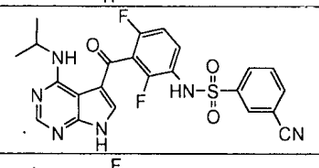
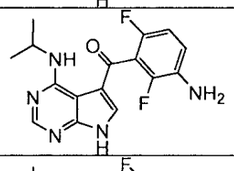
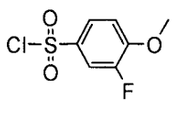
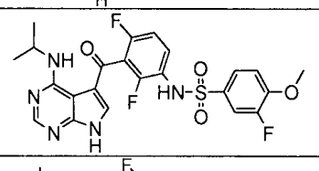
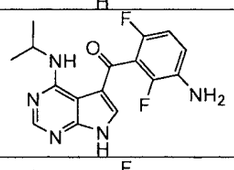
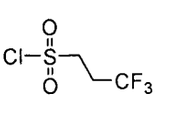
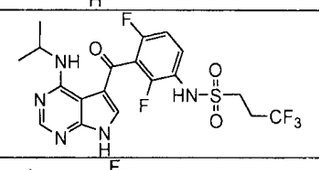
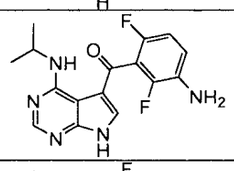
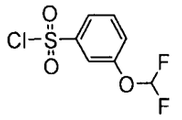
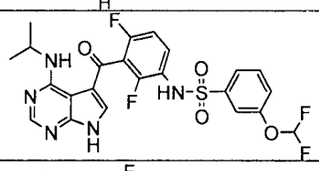
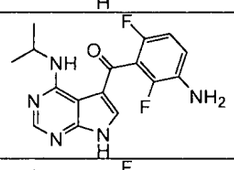
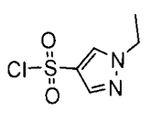
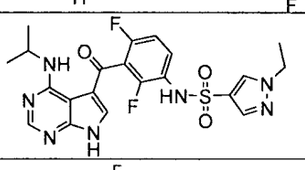
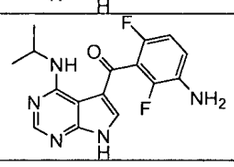
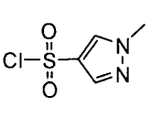
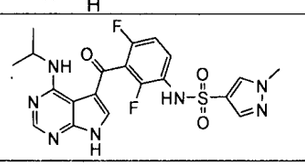
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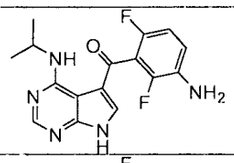
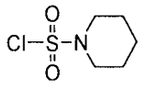
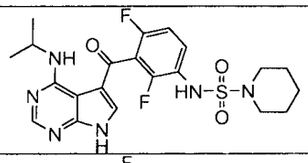
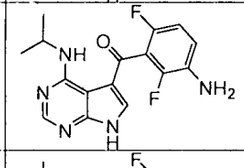
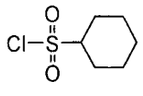
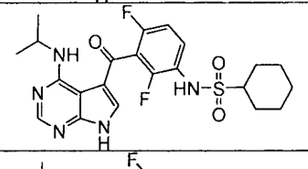
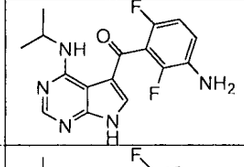
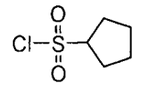
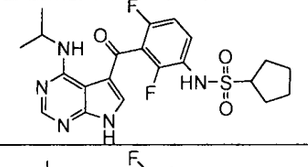
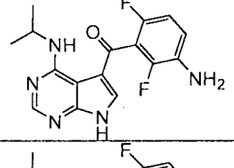
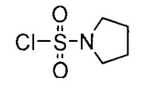
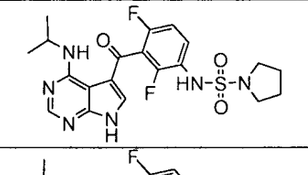
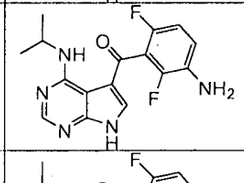
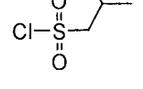
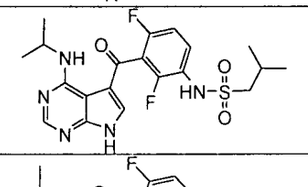
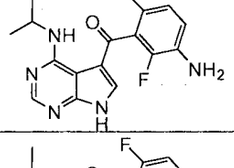
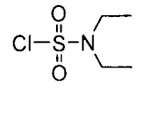
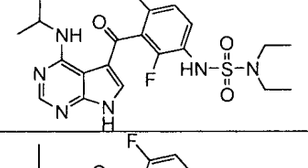
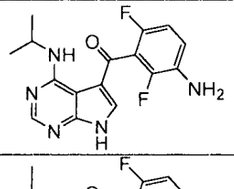
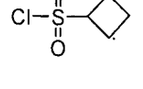
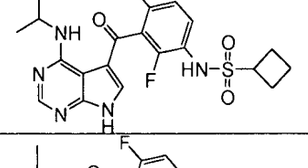
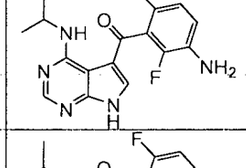
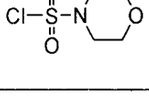
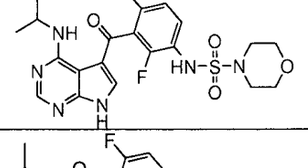
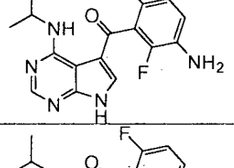
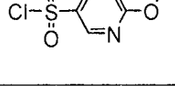
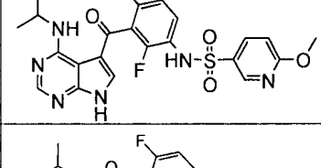
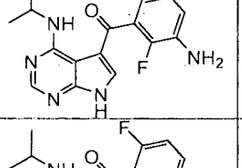
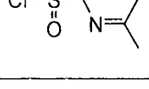
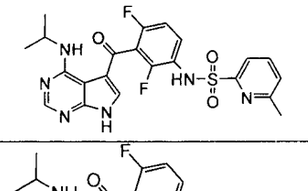
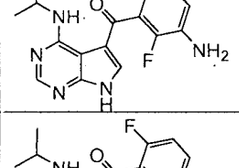
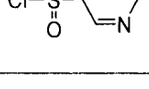
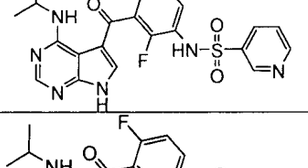
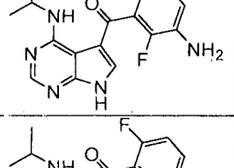
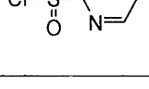
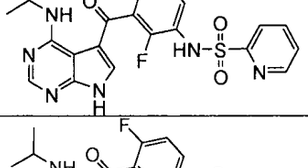
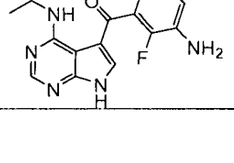
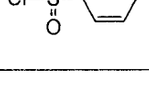
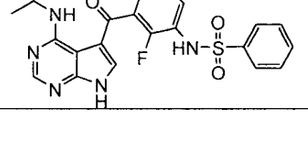
N-[3-(4-Cloro-5-hidroximetil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (**P-2029**), and

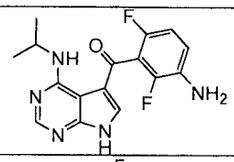
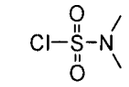
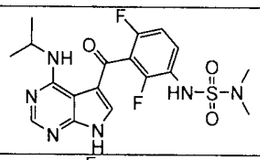
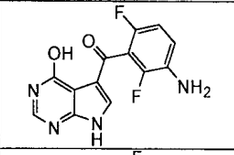
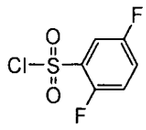
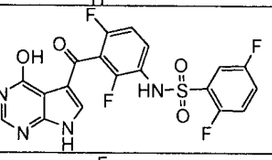
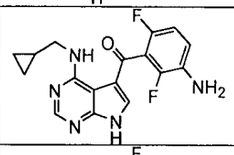
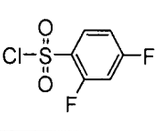
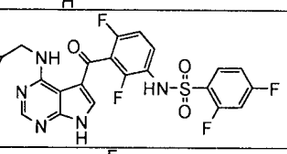
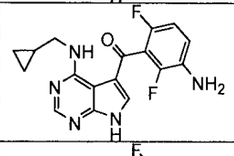
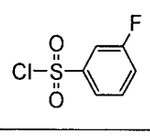
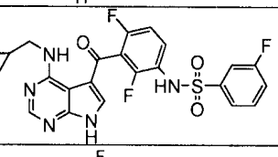
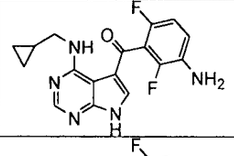
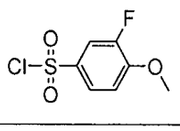
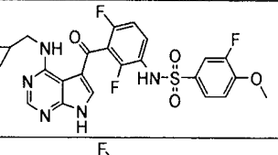
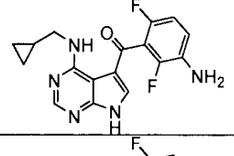
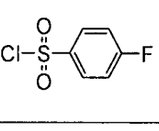
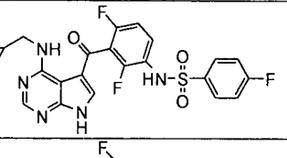
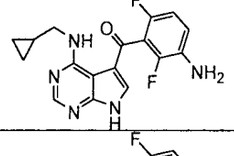
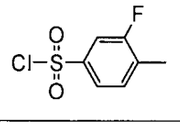
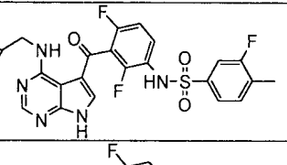
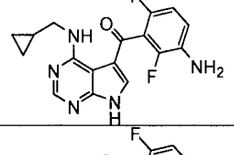
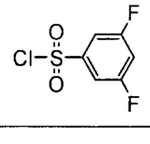
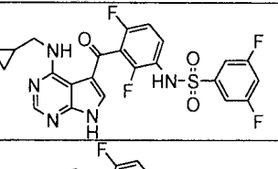
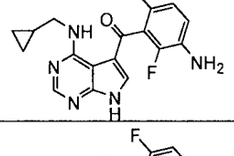
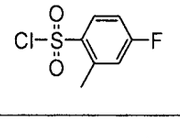
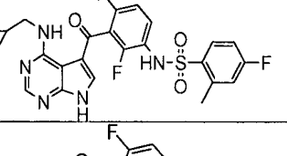
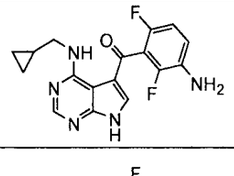
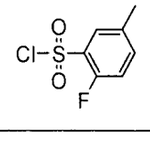
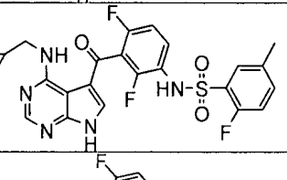
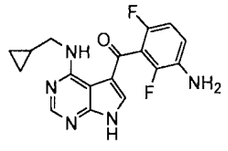
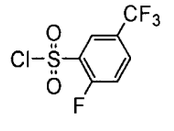
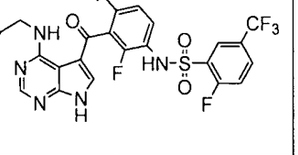
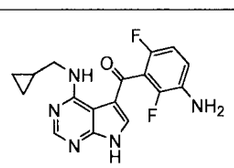
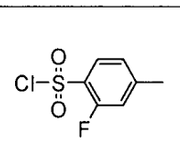
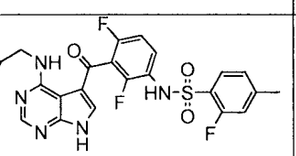
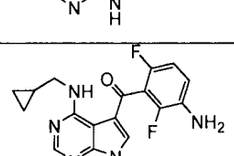
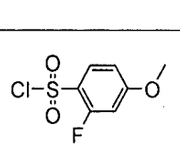
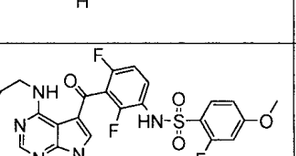
N-[2,4-Difluoro-3-(4-iodo-5-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (**P-2030**).

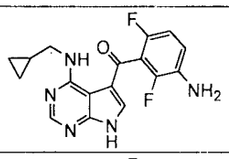
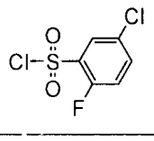
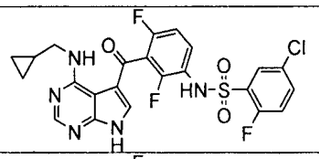
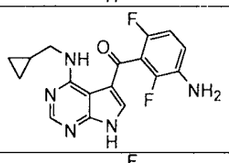
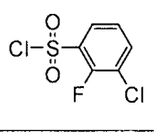
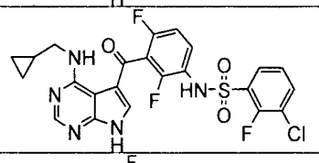
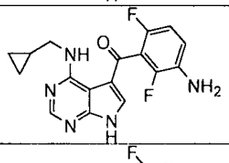
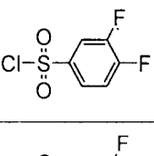
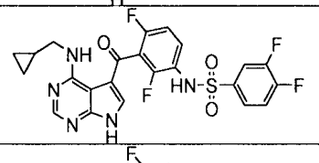
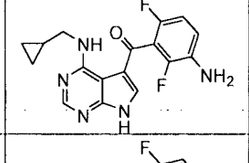
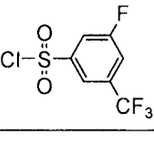
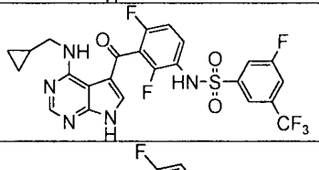
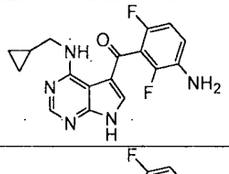
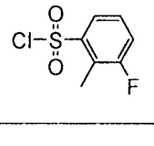
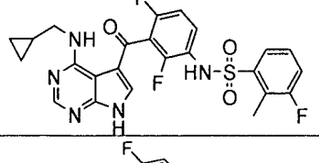
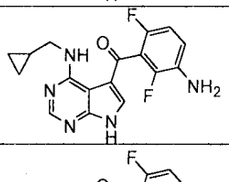
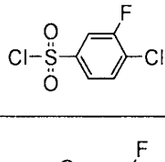
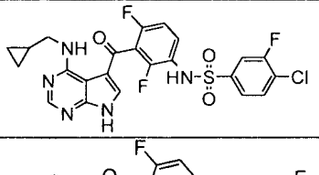
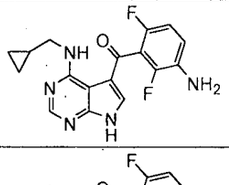
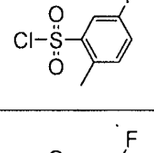
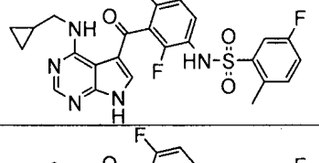
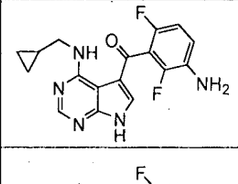
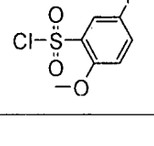
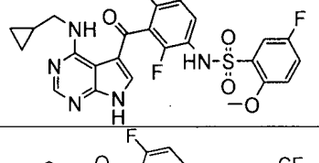
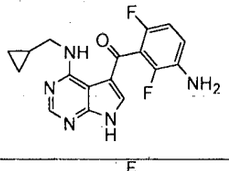
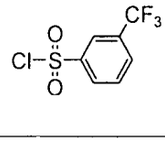
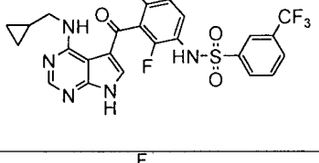
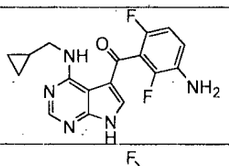
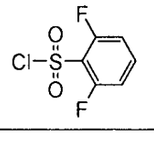
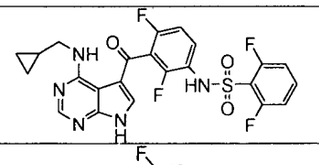
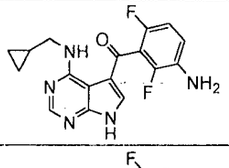
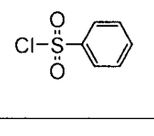
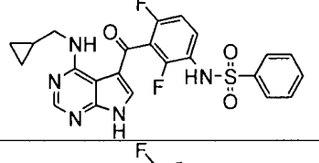
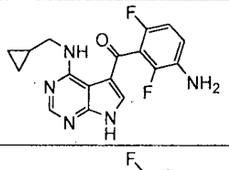
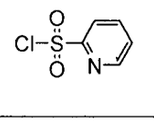
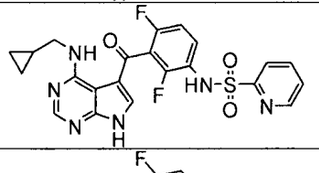
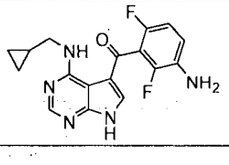
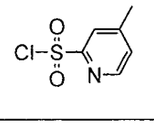
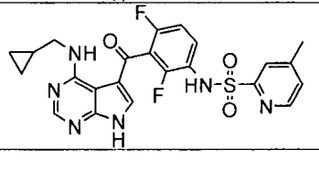
La siguiente tabla indica el compuesto 7H-pirrolo[2,3-d]pirimidina o 1H-pirrolo[2,3-b]piridina (columna 2) y compuesto de cloruro de sulfonilo (columna 3) utilizado para ofrecer el compuesto deseado (columna 4). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 5.

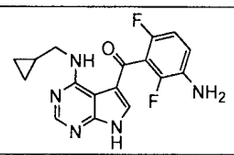
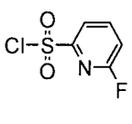
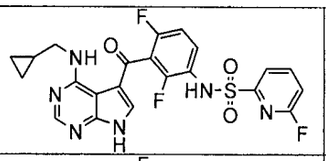
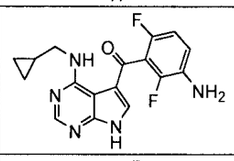
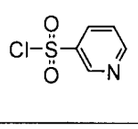
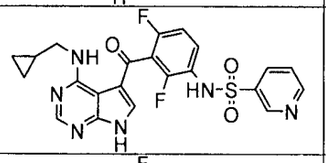
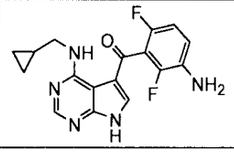
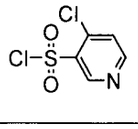
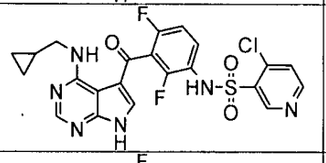
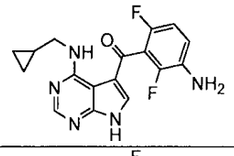
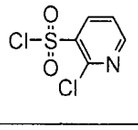
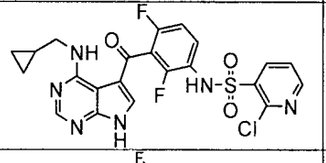
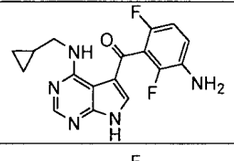
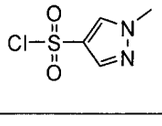
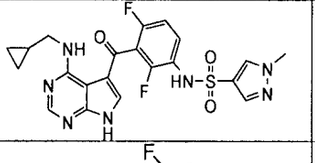
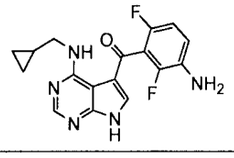
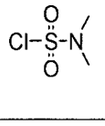
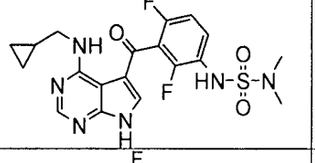
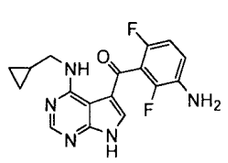
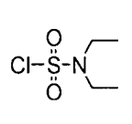
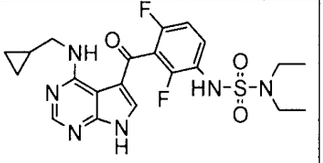
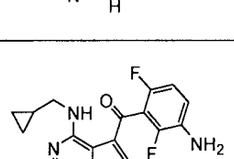
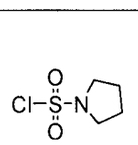
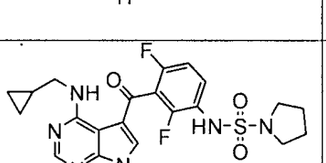
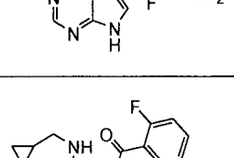
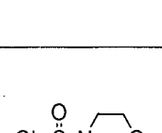
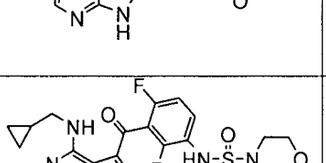
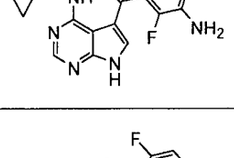
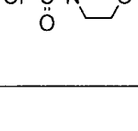
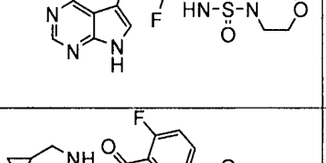
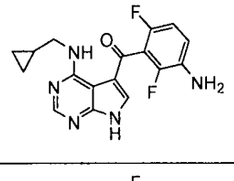
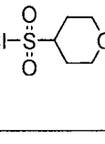
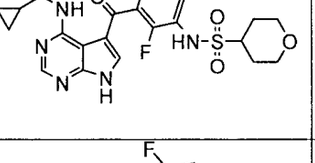
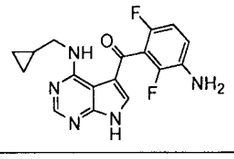
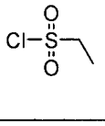
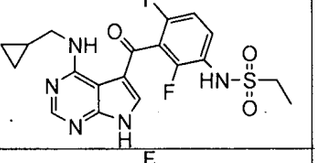
Número de comp.	7H-pirrolo[2,3-d]pirimidina	Cloruro de sulfonilo	Estructura del compuesto	MS (ESI) $[M+H^+]^+$
77				
P-1018				476.0
P-1036				477.0
P-1070				448.9
P-1073				490.0
P-1104				506.0
P-1107				491.4
P-1108				497.5

P-1109				478.0
P-1110				538.5
P-1111				508.0
P-1112				508.0
P-1113				508.0
P-1114				438.0
P-1115				490.5
P-1116				497.5
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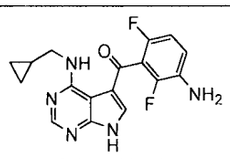
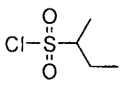
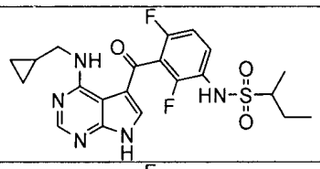
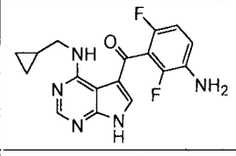
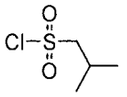
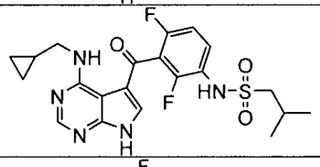
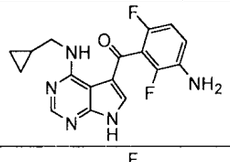
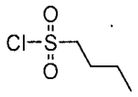
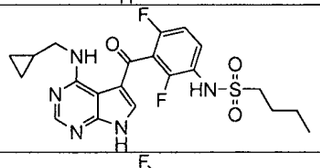
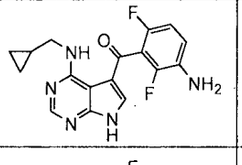
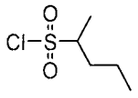
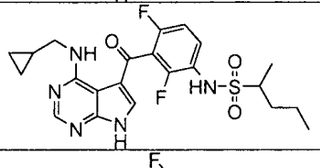
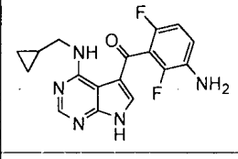
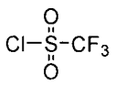
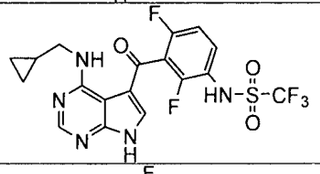
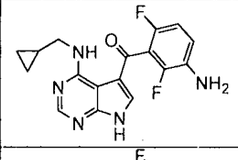
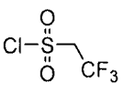
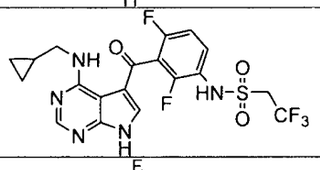
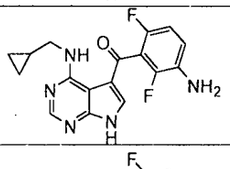
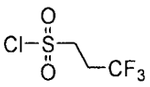
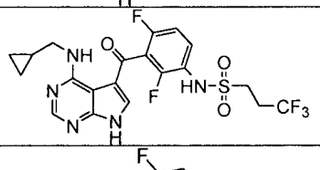
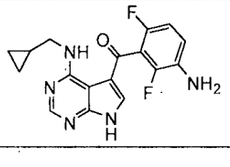
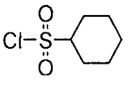
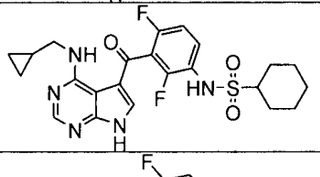
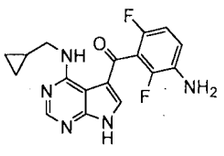
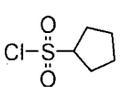
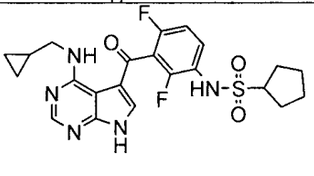
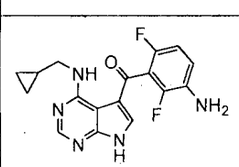
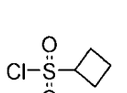
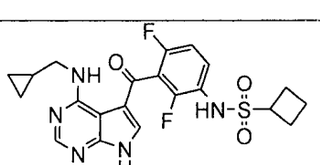
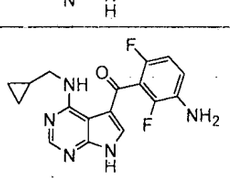
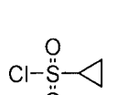
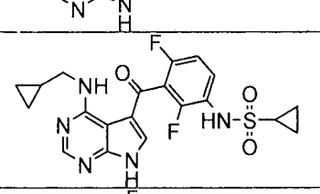
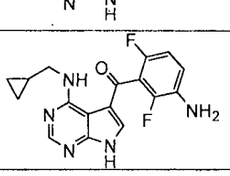
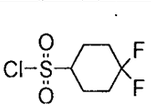
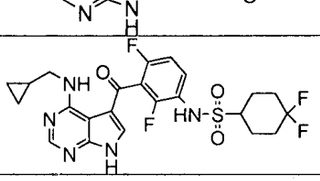
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P-1128				450.0
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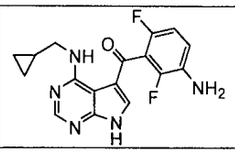
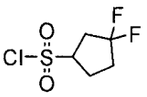
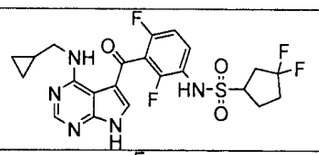
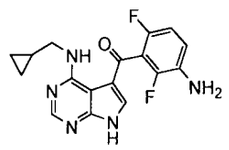
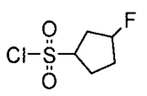
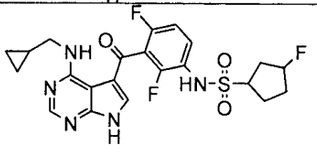
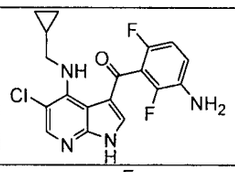
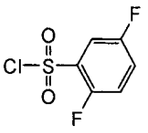
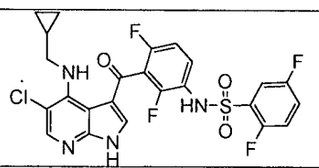
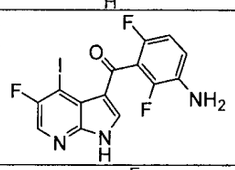
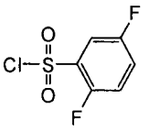
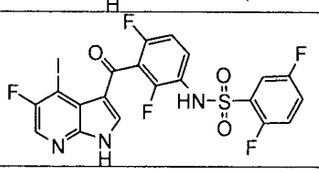
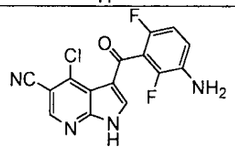
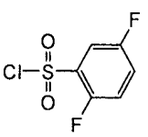
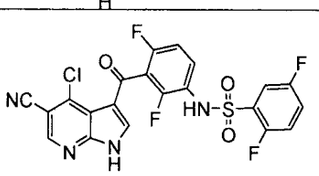
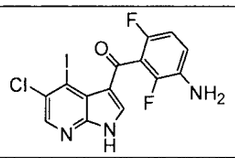
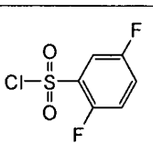
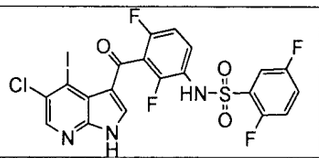
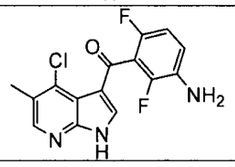
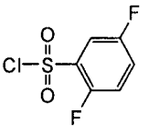
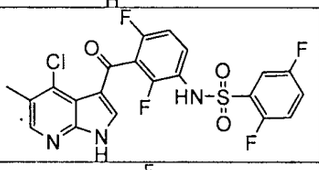
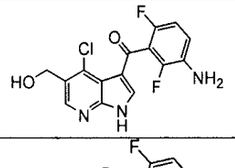
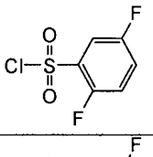
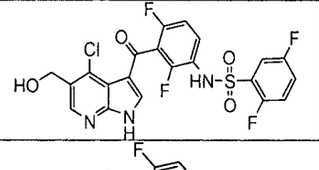
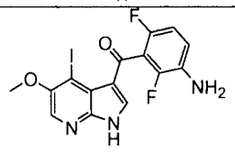
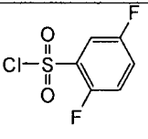
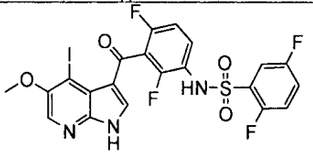
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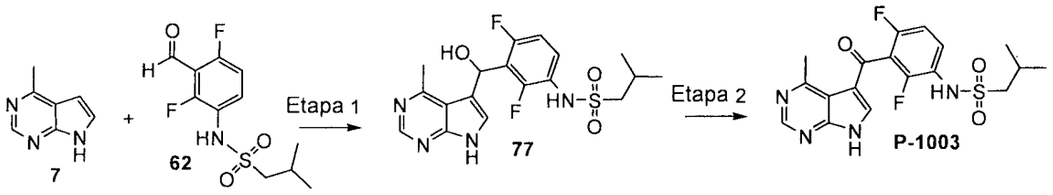
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P-1232				
P-1233				

P-1234				
P-1235				
P-2021				
P-2025				593.8
P-2026				508.9, 510.9
P-2027				
P-2028				
P-2029				
P-2030				

Ejemplo 5: Síntesis de [2,4-difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida del ácido 2-metil-propano-1-sulfónico P-1003.

[0258] La [2,4-difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida del ácido 2-metil-propano-1-sulfónico **P-1003** se prepara en dos etapas a partir de 4-metil-7H-pirrolo[2,3-d]pirimidina **7** y (2,4-difluoro-3-formil-fenil)-amida del ácido 2-metil-propano-1-sulfónico **62** como se muestra en el Esquema 5.

Esquema 5



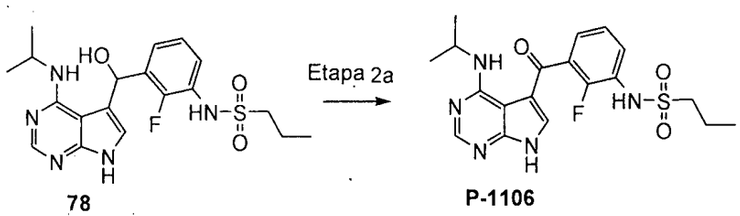
Etapa 1 - Preparación de {2,4-difluoro-3-[hidroxi-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-il)-metil]-fenil}-amida del ácido 2-metil-propano-1-sulfónico (77):

[0259] En un matraz de fondo redondo, 4-metil-7H-pirrolo[2,3-d]pirimidina (7, 97.0 mg, 0.728 mmol) se combina con la (2,4-difluoro-3-formil-fenil)-amida del ácido 2-metil-propano-1-sulfónico (62, 202 mg, 0.728 mmol), hidróxido de potasio (204 mg, 3.64 mmol) y 1.4 ml de metanol. La reacción se agita a temperatura ambiente durante 7 horas. La reacción se neutraliza con ácido clorhídrico acuoso 0.1 N y se extrae 3 x con etil acetato. La capa orgánica combinada se lava con salmuera, se seca con sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía de columna en gel de sílice, eluyendo con etil acetato y diclorometano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (**77**, 113 mg). MS (ESI) $[M-H^+]^-$ = 409.2.

*Etapa 2 - Preparación de [2,4-difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida del ácido 2-metil-propano-1-sulfónico (**P-1003**):*

[0260] A la {2,4-difluoro-3-[hidroxi-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-il)-metil]-fenil}-amida del ácido 2-metil-propano-1-sulfónico (77, 99 mg, 0.24 mmol) en 2 ml de tetrahidrofurano, se agrega periodinano de Dess-Martin (112 mg, 0.265 mmol) y la reacción se agita a temperatura ambiente durante 2 horas. La reacción se vierte en tiosulfato de sodio saturado acuoso en conjunto con algo de bicarbonato de sodio sólido y se extrae con acetato de etilo. La capa orgánica se combina y lava con agua, luego con salmuera, y se seca con sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía de columna en gel de sílice, eluyendo con etil acetato y diclorometano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (**P-1003**, 28 mg). MS (ESI) $[M+H^+]^+$ = 409.3.

[0261] La [2-fluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida del ácido propano-1-sulfónico **P-1106** se prepara de manera similar, al hacer reaccionar isopropil-(7H-pirrolo[2,3-d]pirimidin-4-il)-amina **11** y la (2-fluoro-3-formil-fenil)-amida del ácido propano-1-sulfónico en la Etapa 1, y además hacer reaccionar mediante la siguiente Etapa 2a:



*Etapa 2a - Preparación de la [2-fluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida del ácido propano-1-sulfónico (**P-1106**):*

[0262] A la {2-fluoro-3-[hidroxi-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-il)-metil]-fenil}-amida del ácido propano-1-sulfónico (**78**, 102 mg, 0.242 mmol) en 1 ml de dimetilsulfóxido, se agrega ácido 2-

yodoxibenzoico estabilizado (181 mg, 45%, 0.29 mmol) y la reacción se agita a temperatura ambiente durante 1 hora. La reacción se vierte en agua y se agita durante 30 minutos, y el precipitado se recolecta por filtración. El sólido resultante se disuelve en 2 ml de tetrahidrofurano y se purifica por cromatografía de columna en gel de sílice, eluyendo con acetato de etilo y diclorometano. Las fracciones apropiadas se combinan y concentran bajo vacío para dar el compuesto deseado (**P-1106**, 34 mg). MS (ESI) $[M+H^+]^+$ = 420.0.

[0263] Compuestos adicionales se preparan al seguir el protocolo del Esquema 5. Los compuestos se preparan opcionalmente al sustituir la 4-metil-7H-pirrolo[2,3-d]pirimidina **7**, con una 7H-pirrolo[2,3-d]pirimidina adecuada y opcionalmente sustituir la (2,4-difluoro-3-formil-fenil)-amida del ácido 2-metil-propano-1-sulfónico **62** con un aldehído adecuado en la etapa 1. Los siguientes compuestos se elaboran usando este procedimiento.

N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1001)***,

Ácido propano-1-sulfónico [3-(4-etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida ***(P-1002)***,

ácido 2-Metil-propano-1-sulfónico [2,4-difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida ***(P-1004)***,

N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida ***(P-1005)***,

N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1006)***,

N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida ***(P-1007)***,

N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida ***(P-1009)***,

N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida ***(P-1010)***,

N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1011)***,

N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1012)***,

N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida ***(P-1013)***,

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-isobutil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida ***(P-1014)***,

N-[2,4-Difluoro-3-(4-isobutil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1015)***,

N-[2,4-Difluoro-3-(4-morfolin-4-il-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1017)***,

N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida ***(P-***

1019),

N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida *(P-1020),*

N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-iloxi)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida *(P-1021),*

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida *(P-1022),*

N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3,5-dimetil-bencenosulfonamida *(P-1025),*

N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3,5-dimetil-bencenosulfonamida *(P-1027),*

N-[2,4-Difluoro-3-(4-isobutoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida *(P-1028),*

N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida *(P-1029),*

N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida *(P-1030),*

N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida *(P-1035),*

N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida *(P-1038),*

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida *(P-1042),*

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida *(P-1044),*

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3,5-dimetil-bencenosulfonamida *(P-1045),*

N-[3-(4-Ciclopropilmetoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida *(P-1053),*

N-[2,4-Difluoro-3-(4-pirrolidin-1-il-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida *(P-1061)*

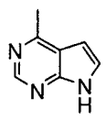
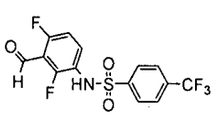
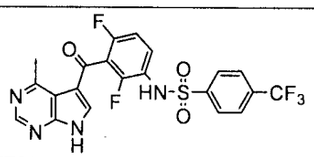
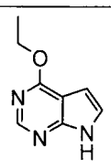
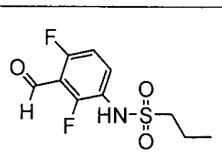
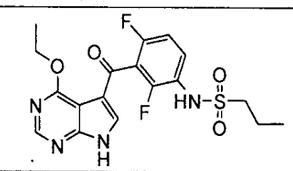
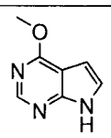
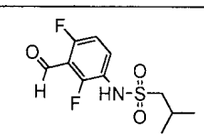
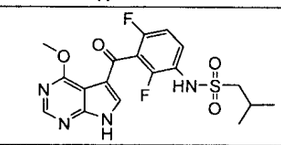
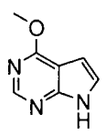
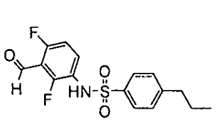
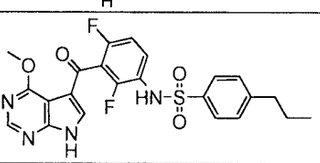
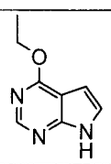
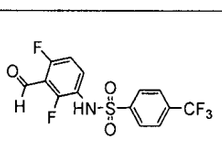
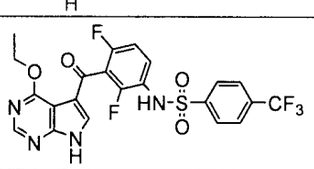
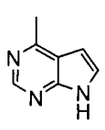
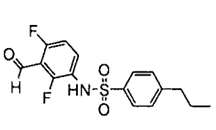
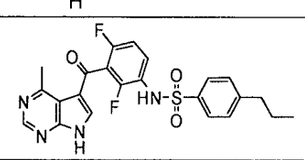
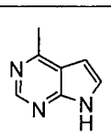
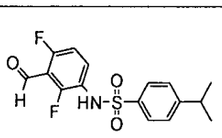
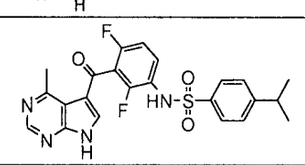
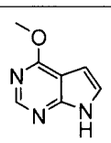
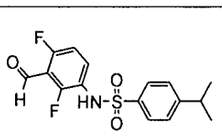
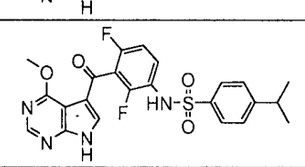
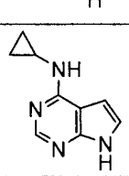
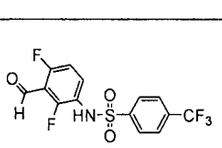
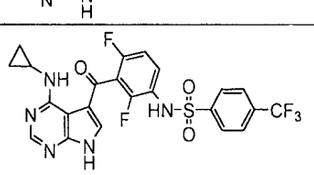
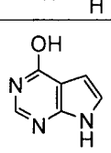
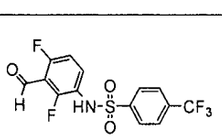
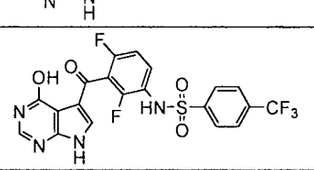
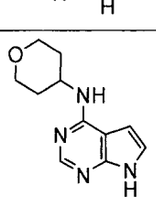
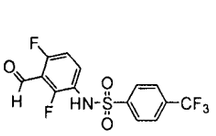
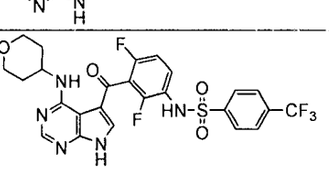
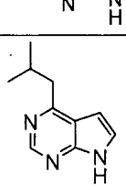
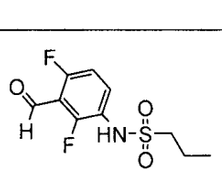
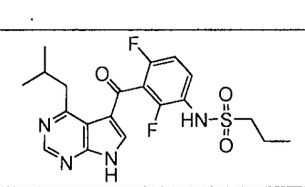
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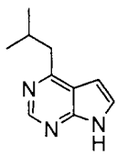
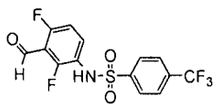
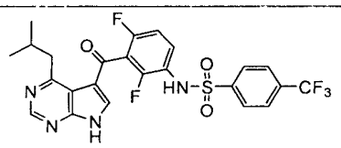
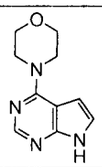
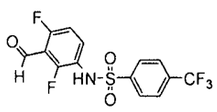
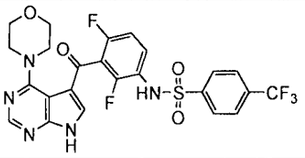
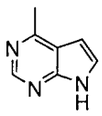
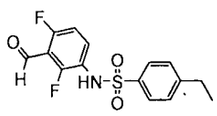
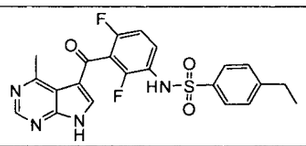
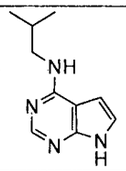
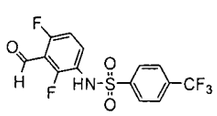
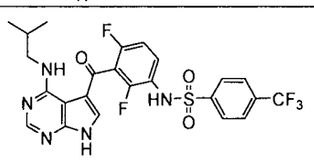
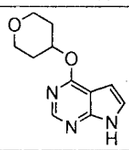
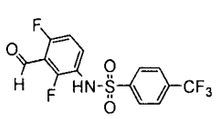
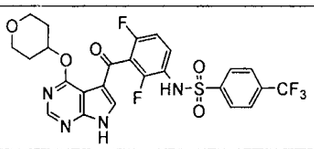
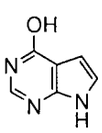
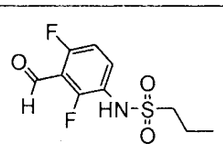
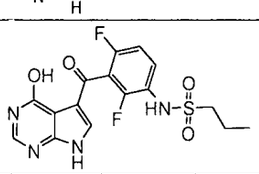
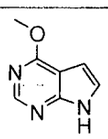
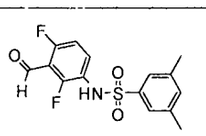
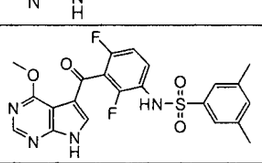
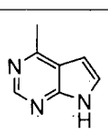
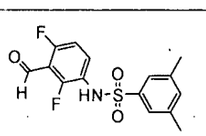
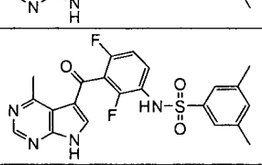
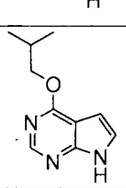
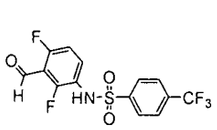
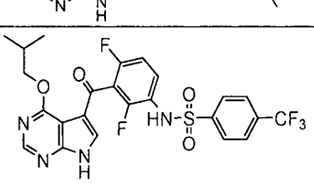
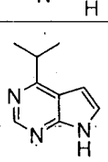
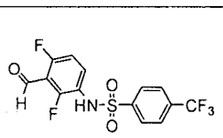
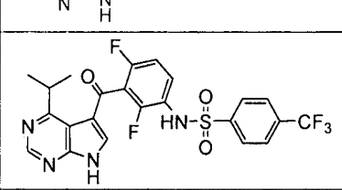
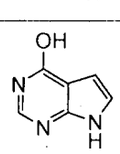
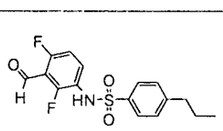
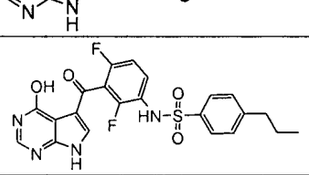
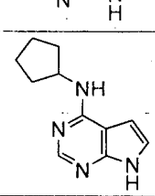
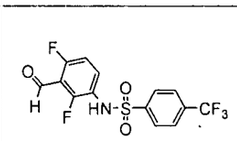
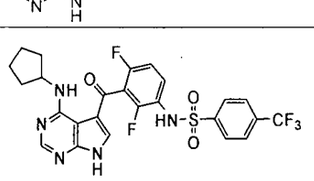
N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida *(P-1182), and*

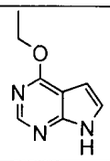
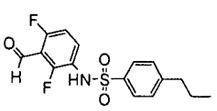
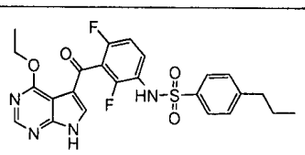
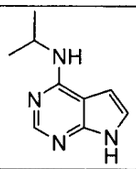
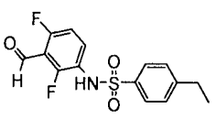
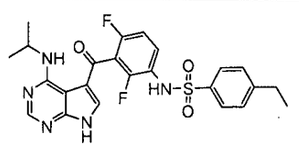
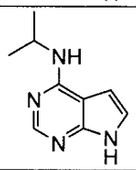
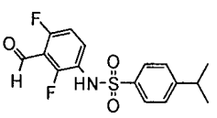
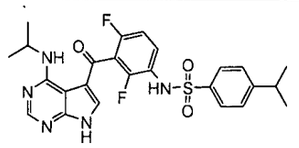
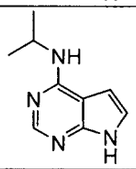
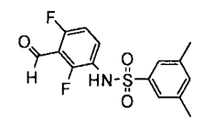
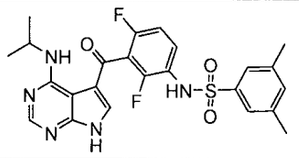
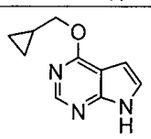
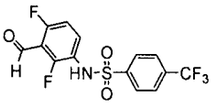
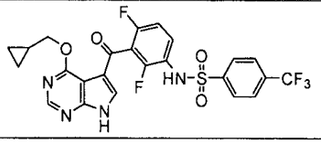
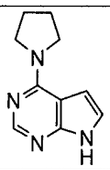
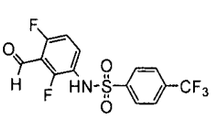
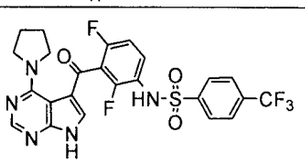
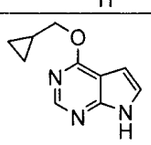
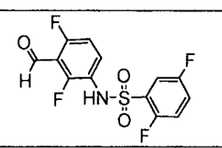
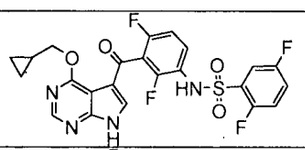
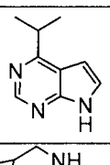
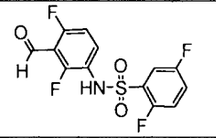
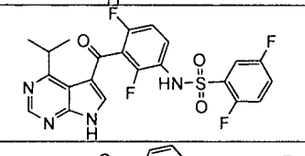
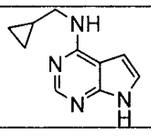
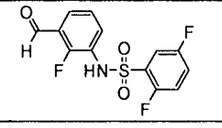
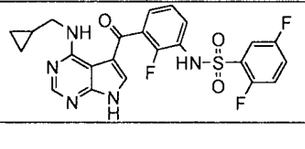
N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2-fluoro-fenil}-2,5-difluoro-bencenosulfonamida *(P-1185).*

La siguiente tabla indica la 7H-pirrolo[2,3-d]pirimidina (columna 2), y compuesto aldehído (columna 3) usado en la etapa 1 para proporcionar el compuesto deseado (columna 4). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 5.

Número	7H-pirrolo[2,3-	Estructura de	Estructura del compuesto	MS (ESI)

de comp.	d]pirimidina	aldehído		$[M+H^+]^+$
P-1001				496.9
P-1002				424.9
P-1004				425.1
P-1005				486.95
P-1006				526.95
P-1007				470.95
P-1009				471.3
P-1010				486.8
P-1011				537.8
P-1012				499.0
P-1013				581.8
P-1014				436.7

P-1015				538.6
P-1017				567.8
P-1019				457.2
P-1020				554.4
P-1021				581.2 $[M-H^+]^-$
P-1022				397.0
P-1025				473.0
P-1027				456.95
P-1028				553.2 $[M-H^+]^-$
P-1029				525.2
P-1030				472.9
P-1035				566.3

P-1038				501.0
P-1042				500.27
P-1044				514.0
P-1045				500.05
P-1053				553.2
P-1061				553.2
P-1181				521.0
P-1182				493.0
P-1185				502.0

[0264] Compuestos adicionales con un centro de 1H-pirrolo[2,3-b]piridina se preparan de manera similar al seguir el protocolo del Esquema 5. Los compuestos se preparan opcionalmente al sustituir la 4-metil-7H-pirrolo[2,3-d]pirimidina **7**, con una 1H-pirrolo[2,3-b]piridina adecuada y opcionalmente sustituir la (2,4-difluoro-3-formil-fenil)-amida del ácido 2-metil-propano-1-sulfónico **62** con un aldehído adecuado en la etapa 1. *Los siguientes compuestos se elaboran usando este procedimiento.*

Ácido propano-1-sulfónico [3-(4-cloro-5-metil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida ***(P-2001)***,

Ácido propano-1-sulfónico [3-(4-cloro-5-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida ***(P-2002)***,

Ácido propano-1-sulfónico [3-(4-ciano-5-fluoro-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida ***(P-2003)***,

Ácido propano-1-sulfónico [3-(4-cloro-5-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-

246

amida ***(P-2004)***,

Ácido propano-1-sulfónico [3-(5-ciano-4-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida ***(P-2005)***,

Ácido propano-1-sulfónico [3-(5-cloro-4-metoxi-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida ***(P-2006)***,

Ácido propano-1-sulfónico [3-(5-cloro-4-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida ***(P-2007)***,

Ácido propano-1-sulfónico [3-(5-cloro-4-metil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida ***(P-2008)***,

N-[3-(4-Ciano-5-fluoro-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida ***(P-2009)***,

N-[3-(5-Cloro-4-ciano-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida ***(P-2010)***,

N-[3-(5-Cloro-4-metil-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida ***(P-2011)***,

Ácido propano-1-sulfónico [3-(4-ciclopentilamino-1H-pirrolo[2,3-b]piridin-3-carbonil)-2,4-difluoro-fenil]-amida ***(P-2012)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(tetrahidro-piran-4-ilamino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-fenil}-amida ***(P-2013)***,

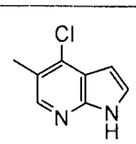
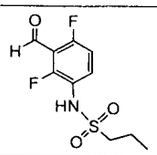
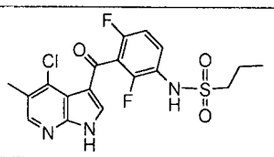
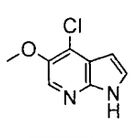
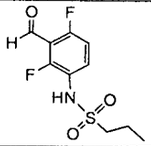
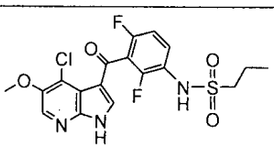
N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida ***(P-2014)***,

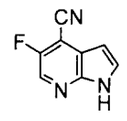
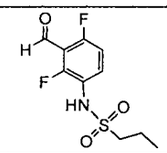
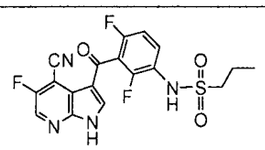
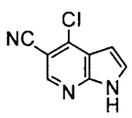
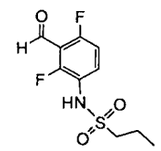
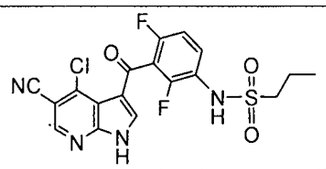
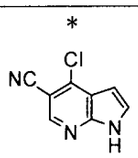
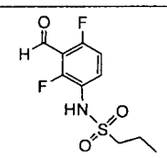
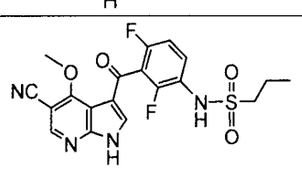
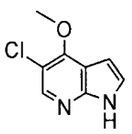
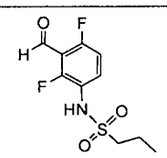
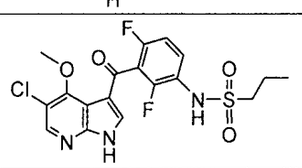
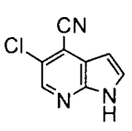
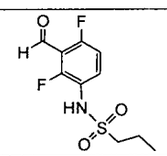
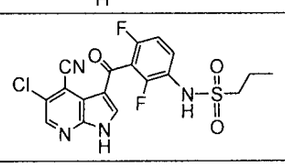
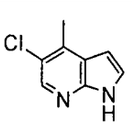
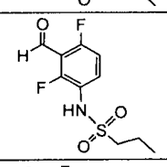
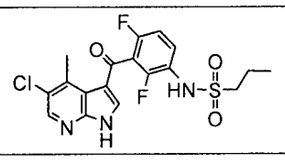
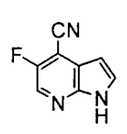
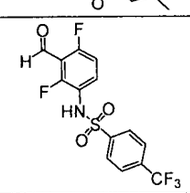
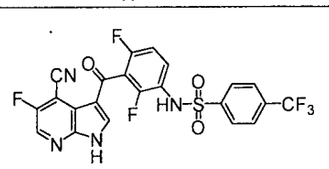
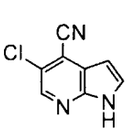
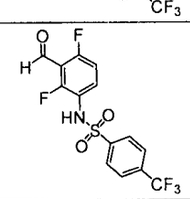
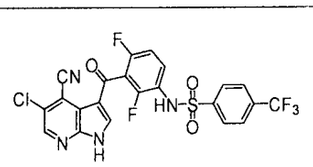
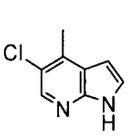
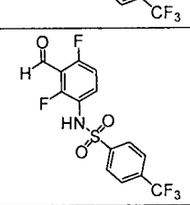
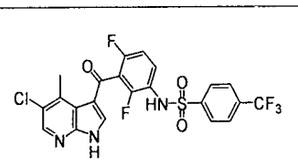
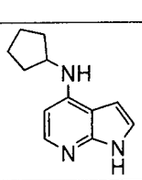
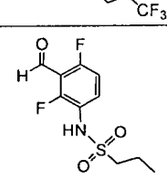
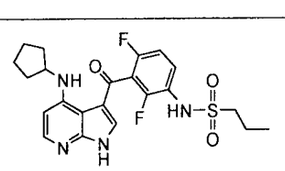
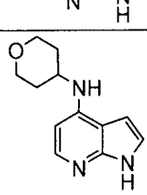
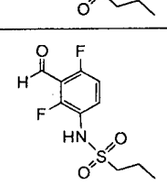
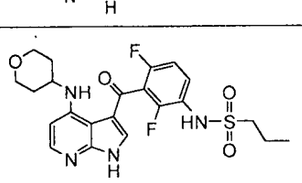
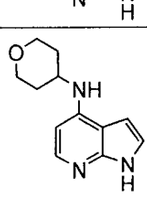
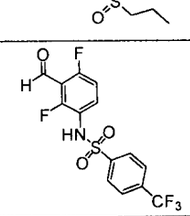
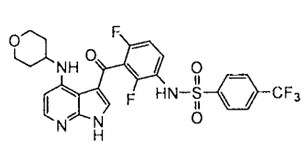
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-amida ***(P-2015)***,

N-[2,4-Difluoro-3-(4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida ***(P-2016)***, *and*

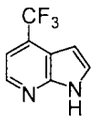
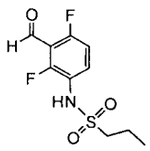
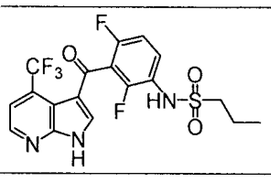
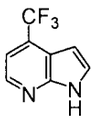
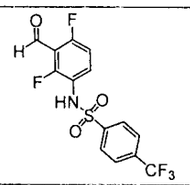
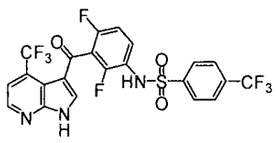
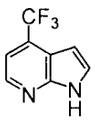
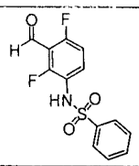
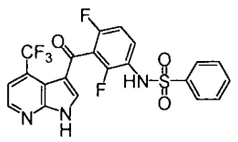
N-[2,4-Difluoro-3-(4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-bencenosulfonamida ***(P-2017)***.

La siguiente tabla indica el compuesto 1H-pirrolo[2,3-b]piridina (columna 2) y el compuesto aldehído (columna 3) usado en la etapa 1 para proporcionar el compuesto deseado (columna 4). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 5.

Número de comp.	1H-pirrolo[2,3-b]piridina	Estructura de aldehído	Estructura del compuesto	MS (ESI) $[M+H^+]^+$
P-2001				427.9 429.9
P-2002				443.9 446.1

P-2003				421.4 $[M-H^+]^-$
P-2004				439.1
P-2005				435.1
P-2006				444.1
P-2007				437.4 439.5
P-2008				428.1 430.1
P-2009				523.3 $[M-H^+]^-$
P-2010				539.3 541.3 $[M-H^+]^-$
P-2011				530.0 532.4
P-2012				463.8
P-2013				479.1
P-2014				581.4

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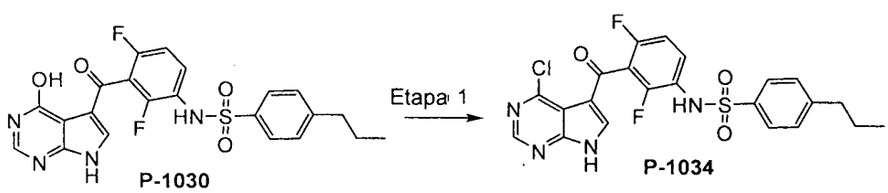
P-2015				447.9
P-2016				549.9
P-2017				481.9

* Durante la reacción, el 4-cloro también se desplazó por el metanol para formar el análogo 4-metoxi en la etapa 1 en la síntesis de **P-2004**, lo cual se lleva a través de la etapa 2 para formar **P-2005**.

Ejemplo 6: Síntesis de N-[3-(4-cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida P-1034.

[0265] La N-[3-(4-cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida **P-1034** se sintetiza en una etapa a partir de N-[2,4-difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida **P-1030** como se muestra en el Esquema 6.

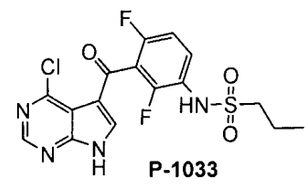
Esquema 6

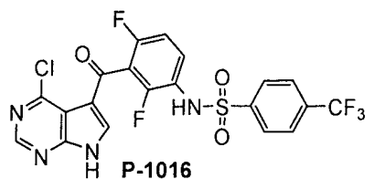


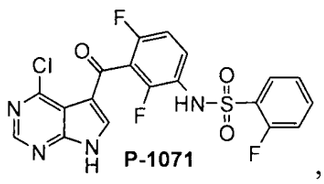
*Etapa 1 - Preparación de N-[3-(4-cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (**P-1034**).*

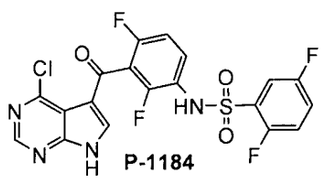
[0266] A N-[2,4-difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida (**P-1030**, 239 mg, 0.506 mmol), se agrega cloruro de fosforilo (4.0 ml, 43 mmol) y la suspensión se calienta en un baño de aceite a 100 °C durante una hora. La reacción se deja enfriar, entonces se vierte en hielo. El sólido resultante se recolecta por filtración de vacío y se seca para proporcionar el compuesto deseado (**P-1030**, 218 mg). MS (ESI) $[M+H^+]^+ = 490.9$.

[0267] La [3-(4-cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida del ácido propan-1-sulfónico **P-1033** y N-[3-(4-cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida **P-1016**, N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida **P-1071**, y N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida **P-1184**,


P-1033 ,


P-1016 ,


P-1071 , y

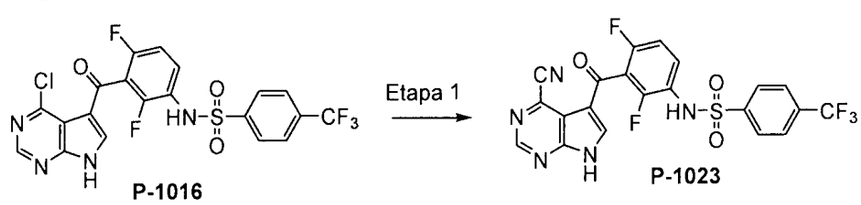

P-1184

se preparan de manera similar al protocolo del Esquema 6 a partir de [2,4-difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida del ácido propan-1-sulfónico **P-1022**, N-[2,4-difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida **P-1012**, N-[2,4-difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida **P-1070**, y N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida **P-1183**, respectivamente. MS (ESI) $[M+H^+]^+$ = 414.8 (**P-1033**), 516.9 (**P-1016**), 466.9, 468.9 (**P-1071**), y 484.9, 486.9 (**P-1184**).

Ejemplo 7: Síntesis de N-[3-(4-ciano-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida P-1023.

[0268] La N-[3-(4-ciano-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida **P-1023** se sintetiza en una etapa a partir de N-[3-(4-cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida **P-1016** como se muestra en el Esquema 7.

Esquema 7



*Etapa 1 - Preparación de N-[3-(4-ciano-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1023**).*

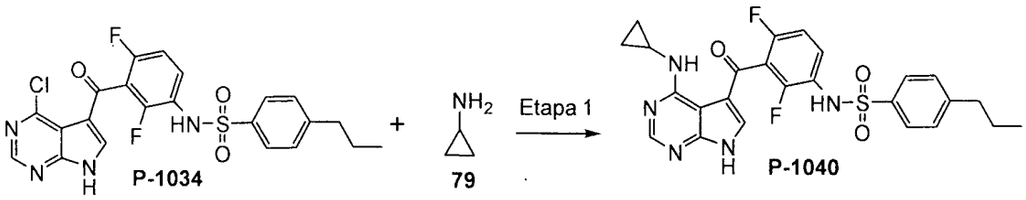
[0269] A N-[3-(4-cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (**P-1016**, 62 mg, 0.12 mmol), se agrega 1.00 ml de dimetil sulfóxido, seguido por cianuro de potasio (39.0 mg, 0.60 mmol). La reacción se calienta a 150 °C en un baño de aceite durante 4 horas, entonces a 150 °C durante la noche. La reacción se vierte en agua y se extrae con acetato de etilo. La capa orgánica se concentra bajo vacío y se purifica por cromatografía de columna en gel de sílice, eluyendo con un gradiente de 10-60% de acetato de etilo en hexanos. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (**P-1023**, 8 mg). MS (ESI) $[M+H^+]^+$ = 508.1.

247 248

Ejemplo 8: Síntesis de N-[3-(4-ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida P-1040.

[0270] La N-[3-(4-ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida **P-1040** se sintetiza en una etapa a partir de N-[3-(4-cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida **P-1034** como se muestra en el Esquema 8.

Esquema 8



*Etapa 1 - Preparación de N-[3-(4-ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (**P-1040**).*

[0271] A N-[3-(4-cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (**P-1034**, 50 mg, 0.10 mmol), se agregan 0.702 ml de alcohol isopropílico, seguido por ciclopropilamina (**79**, 0.0357 ml, 70% de solución acuosa, 0.509 mmol). La reacción se calienta a 80 °C en un baño de aceite durante 17 horas, entonces se vierte en agua y salmuera y se extrae con acetato de etilo. La capa orgánica se seca sobre sulfato de magnesio, se filtra y el filtrado se concentra bajo vacío para proporcionar el compuesto deseado (**P-1040**, 52 mg). MS (ESI) $[M+H^+]^+ = 512.0$.

[0272] Compuestos adicionales se preparan al seguir el protocolo del Esquema 8. En algunos casos, sin limitación, el compuesto de *4-cloro*-7H-pirrolo[2,3-d]pirimidina (o compuesto de 1H-pirrolo[2,3-b]piridina similar 4-halógeno sustituida) se hace reaccionar directamente en el compuesto amina líquido sin solvente adicional (por ejemplo, alcohol isopropílico). En algunos casos, sin limitación, la mezcla de reacción incluye trietilamina. Los compuestos puede purificarse además por técnicas estándar, tales como cromatografía en gel de sílice o HPLC. Los compuestos se preparan opcionalmente al sustituir la N-[3-(4-cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida **P-1034** con un compuesto adecuado 4-cloro-7H-pirrolo[2,3-d]pirimidina o compuesto 4-halo-1H-pirrolo[2,3-b]piridina y opcionalmente sustituir la ciclopropilamina 79 con una amina adecuada en la etapa 1. *Los siguientes compuestos se elaboran usando este procedimiento.*

N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida ***(P-1013)***,

N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1020)***,

N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1024)***,

N-[2,4-Difluoro-3-(4-metilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1026)***,

N-[3-(4-Amino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1031)***,

N-[2,4-Difluoro-3-(4-propilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1032)***,

N-[2,4-Difluoro-3-(4-fenilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1037)***,

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1039)***,

Ácido propano-1-sulfónico [3-(4-ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida ***(P-1041)***,

N-{2,4-Difluoro-3-[4-(2-hidroxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida ***(P-1043)***,

N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-propil-bencenosulfonamida ***(P-1046)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(tetrahidro-piran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1047)***,

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-fenilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida ***(P-1048)***,

N-[3-(4-Dimetilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1049)***,

N-{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida ***(P-1050)***,

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida ***(P-1051)***,

N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida ***(P-1052)***,

N-{2,4-Difluoro-3-[4-(tetrahidro-furan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida ***(P-1054)***,

N-[2,4-Difluoro-3-(4-isopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida ***(P-1055)***,

N-{2,4-Difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-propil-bencenosulfonamida ***(P-1056)***,

N-{2,4-Difluoro-3-[4-(1-metil-piperidin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida ***(P-1057)***,

N-{2,4-Difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida ***(P-1058)***,

N-{3-[4-(2-Dimetilamino-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida ***(P-1059)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(oxetan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1060)***,

N-[2,4-Difluoro-3-(4-pirrolidin-1-il-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1061)***,

N-{2,4-Difluoro-3-[4-(1-metil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-

trifluorometil-bencenosulfonamida ***(P-1062)***,

N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-4-trifluorometil-bencenosulfonamida ***(P-1063)***,

N-[2,4-Difluoro-3-(4-hidroxiamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida ***(P-1064)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(4-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1065)***,

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-hidrazino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida ***(P-1066)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(naftalen-2-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1067)***,

Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[(oxetan-3-ilmetil)-amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida ***(P-1068)***,

N-{2,4-Difluoro-3-[4-(4-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida ***(P-1069)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(naftalen-1-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1072)***,

Ácido propano-1-sulfónico [3-(4-bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida ***(P-1074)***,

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-propilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida ***(P-1075)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(piridin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1076)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(piridin-2-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1077)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1078)***,

Ácido propano-1-sulfónico {3-[4-(ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida ***(P-1079)***,

Ácido propano-1-sulfónico {3-[4-(1-benzil-pirrolidin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida ***(P-1080)***,

Ácido propano-1-sulfónico [3-(4-ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida ***(P-1081)***,

Ácido propano-1-sulfónico [3-(4-etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida ***(P-1082)***,

Ácido propano-1-sulfónico {3-[4-(3-dimetilamino-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida ***(P-1083)***,

{3-[4-(3-cloro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida del ácido propano-1-sulfónico ***(P-1084)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1085)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1086)***,

Ácido propano-1-sulfónico {3-[4-(4-cloro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida ***(P-1087)***,

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida ***(P-1088)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(4-trifluorometil-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1089)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(6-metoxi-piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1090)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-trifluorometil-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1091)***,

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida ***(P-1092)***,

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-p-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida ***(P-1093)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-fluoro-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1094)***,

Ácido propano-1-sulfónico {3-[4-(1-etil-piperidin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida ***(P-1095)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1-metanosulfonil-piperidin-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1096)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(tetrahidro-furan-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1097)***,

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-metilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida ***(P-1098)***,

Ácido propano-1-sulfónico {3-[4-(1-etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida ***(P-1099)***,

Ácido propano-1-sulfónico {3-[4-(1,3-dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida ***(P-1100)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(2-fluoro-4-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1101)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1-metil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1102)***,

N-[3-(4-Ciclopropilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida ***(P-1103)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-fluoro-5-metoxi-piridin-2-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1105)***,

Ácido propano-1-sulfónico {3-[4-(benzo[1,2,5]tiadiazol-5-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida ***(P-1134)***,

N-[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-

250

bencenosulfonamida ***(P-1135)***,

N-{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida ***(P-1136)***,

N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida ***(P-1137)***,

N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida ***(P-1138)***,

N-{2,4-Difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2,5-difluoro-bencenosulfonamida ***(P-1139)***,

N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida ***(P-1140)***,

N-[2,4-Difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida ***(P-1141)***,

N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida ***(P-1142)***,

N-{3-[4-(1,3-Dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida ***(P-1143)***,

N-[3-(4-Bencilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida ***(P-1144)***,

N-{2,4-Difluoro-3-[4-(piridin-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida ***(P-1145)***,

N-{3-[4-(Ciclopropilmetil-amino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida ***(P-1146)***,

N-[3-(4-Ciclopentilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida ***(P-1147)***,

N-[3-(4-Etilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida ***(P-1148)***,

N-{2,4-Difluoro-3-[4-(3-metoxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida ***(P-1149)***,

N-{2,4-Difluoro-3-[4-(2-metoxi-etilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-2-fluoro-bencenosulfonamida ***(P-1150)***,

N-[2,4-Difluoro-3-(4-isobutilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida ***(P-1151)***,

N-[2,4-Difluoro-3-(4-m-tolilamino-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida ***(P-1152)***,

N-{3-[4-(1-Etil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida ***(P-1153)***,

N-{3-[4-(1,3-Dimetil-1H-pirazol-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-2-fluoro-bencenosulfonamida ***(P-1154)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1H-indazol-6-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1157)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(1H-indazol-5-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1158)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(4-hidroxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1159)***,

Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[(5-metil-1H-pirazol-3-ilmetil)-amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida ***(P-1160)***,

ácido 3-({5-[2,6-Difluoro-3-(propano-1-sulfonilamino)-benzoil]-7H-pirrolo[2,3-d]pirimidin-4-ilamino}-metil)-benzoico ***(P-1161)***,

metil éster del ácido 4-{5-[2,6-Difluoro-3-(propano-1-sulfonilamino)-benzoil]-7H-pirrolo[2,3-d]pirimidin-4-ilamino}-benzoico ***(P-1162)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-[1,2,4]triazol-1-il-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1164)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-oxazol-5-il-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1165)***,

Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[(piridin-3-ilmetil)-amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida ***(P-1166)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-[1,2,4]triazol-1-il-propilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1167)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-piridin-3-il-propilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1168)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(3-hidroxi-fenilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1169)***,

Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(5-metil-4H-[1,2,4]triazol-3-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida ***(P-1170)***,

Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(5-metil-tetrazol-1-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida ***(P-1171)***,

Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(4H-[1,2,4]triazol-3-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida ***(P-1172)***,

Ácido propano-1-sulfónico (3-{4-[(benzo[1,2,5]oxadiazol-5-ilmetil)-amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-2,4-difluoro-fenil)-amida ***(P-1173)***,

Ácido propano-1-sulfónico {3-[4-(1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida ***(P-1174)***,

Ácido propano-1-sulfónico {3-[4-(1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-2,4-difluoro-fenil}-amida ***(P-1175)***,

Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[2-(5-metil-4H-[1,2,4]triazol-3-il)-etilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida ***(P-1176)***,

Ácido propano-1-sulfónico {2,4-difluoro-3-[4-(2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilamino)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-amida ***(P-1177)***,

Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(2-metil-2H-tetrazol-5-il)-fenilamino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida ***(P-1178)***,

Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[3-(5-metil-[1,3,4]oxadiazol-2-il)-fenilamino]-7H-

pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida ***(P-1179)***,

Ácido propano-1-sulfónico (2,4-difluoro-3-{4-[(piridazin-4-ilmetil)-amino]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-fenil)-amida ***(P-1180)***,

N-{3-[4-(Ciclopropilmetil-amino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida ***(P-2018)***,

N-{3-[4-(Ciclopropilmetil-amino)-5-fluoro-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida ***(P-2019)***,

N-{3-[5-Ciano-4-(ciclopropilmetil-amino)-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida ***(P-2020)***,

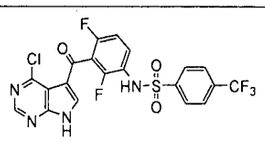
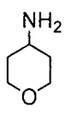
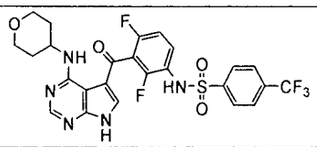
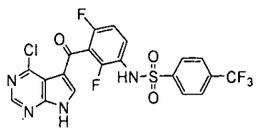
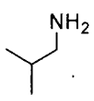
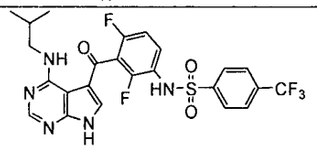
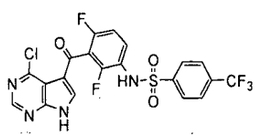
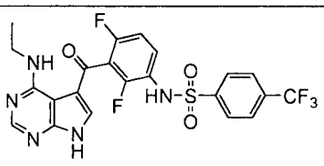
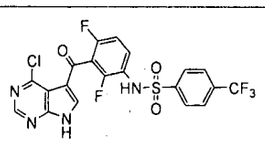
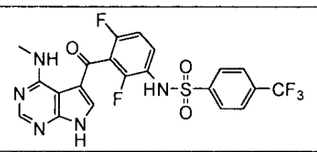
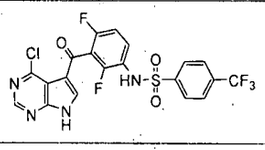
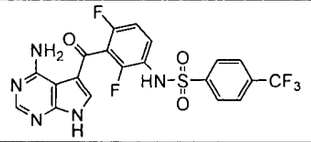
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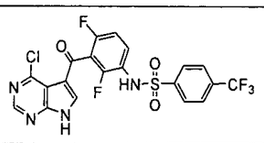
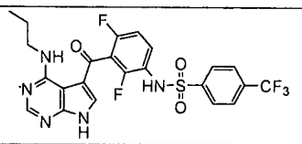
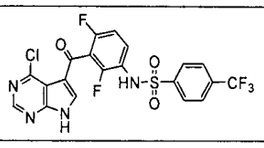
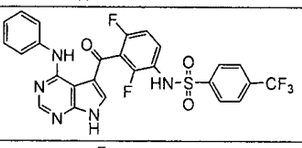
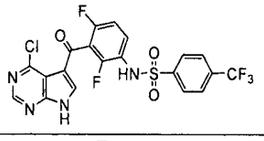
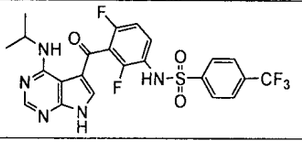
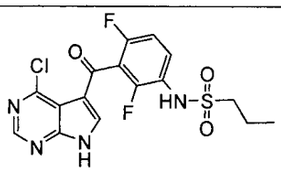
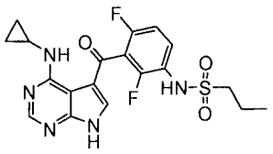
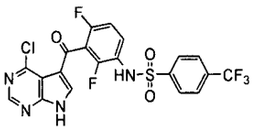
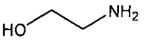
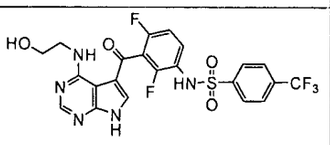
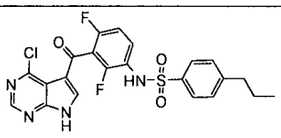
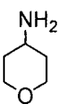
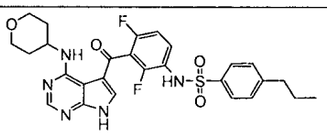
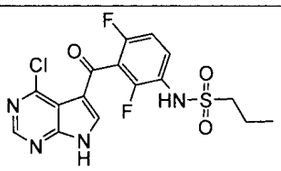
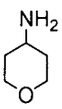
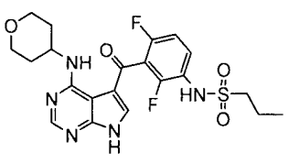
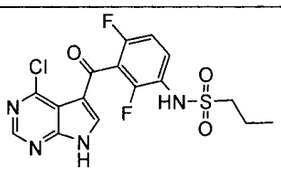
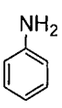
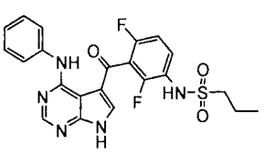
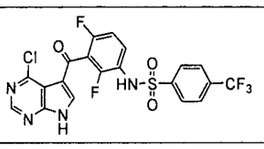
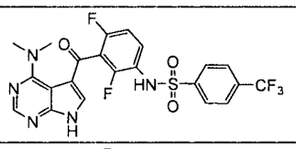
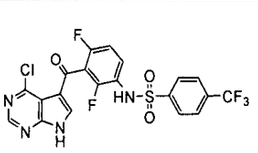
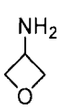
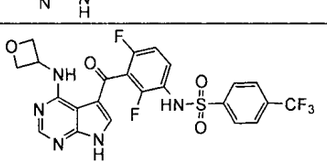
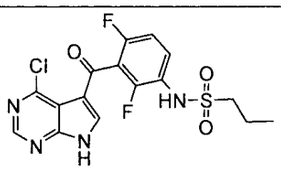
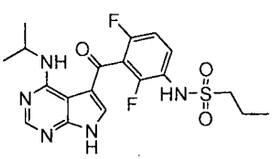
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N-{3-[4-(Ciclopropilmetil-amino)-5-hidroximetil-1H-pirrolo[2,3-b]piridin-3-carbonil]-2,4-difluoro-fenil}-2,5-difluoro-bencenosulfonamida ***(P-2023)***,

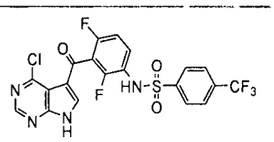
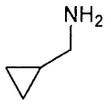
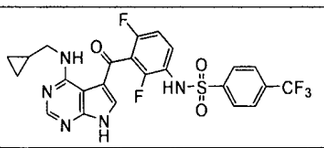
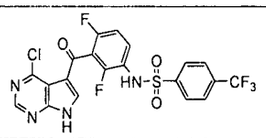
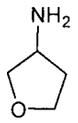
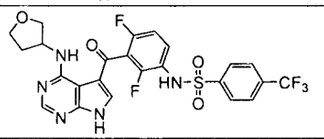
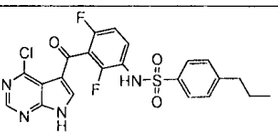
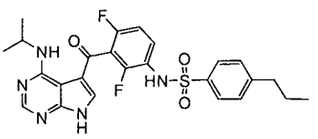
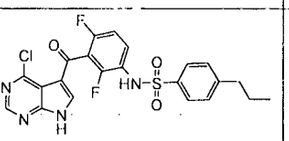
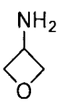
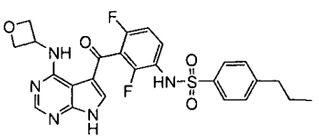
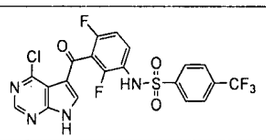
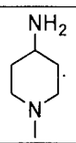
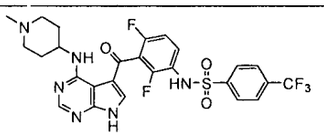
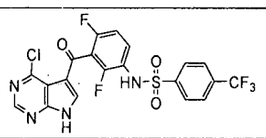
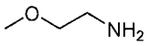
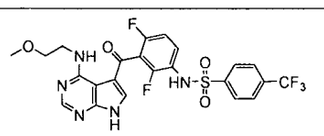
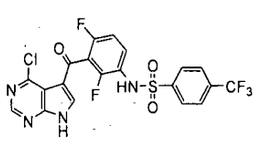
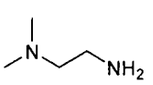
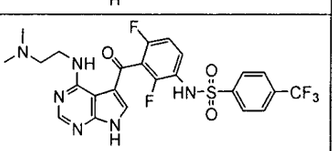
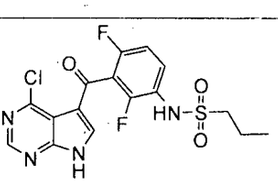
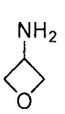
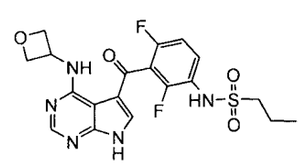
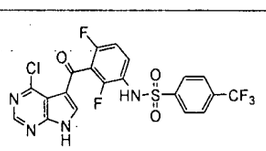
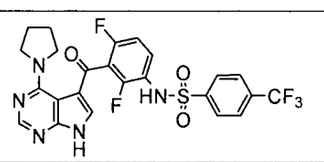
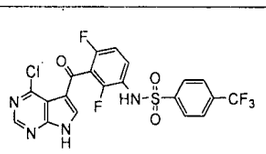
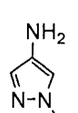
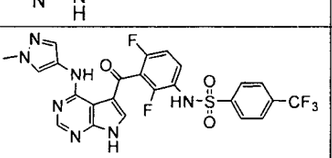
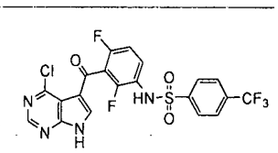
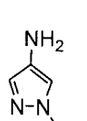
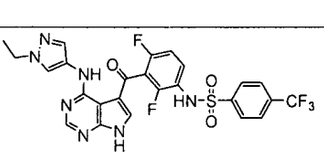
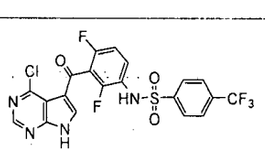
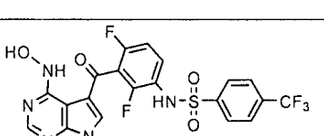
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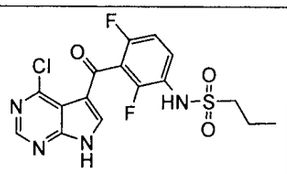
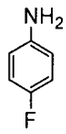
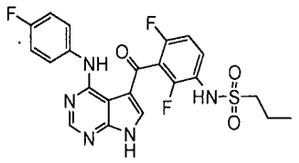
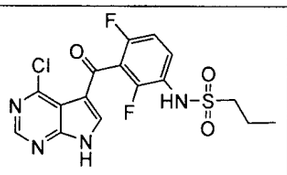
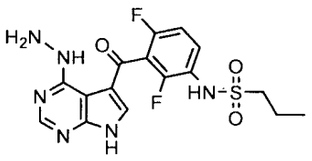
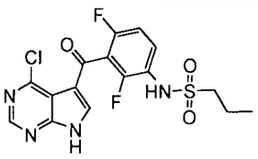
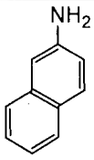
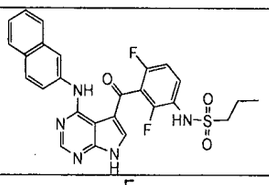
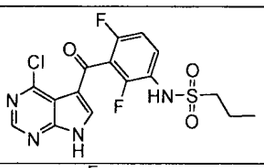
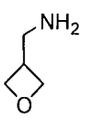
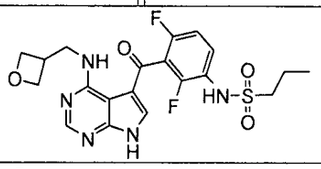
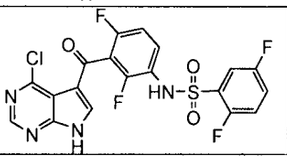
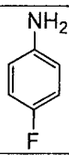
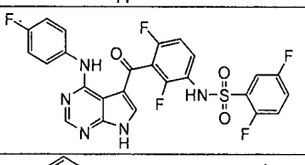
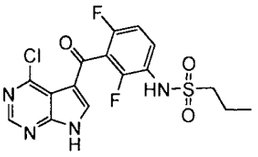
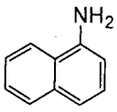
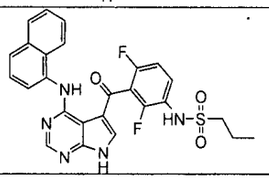
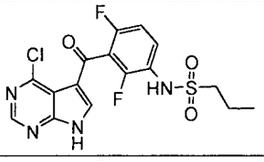
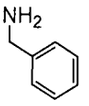
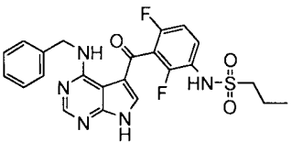
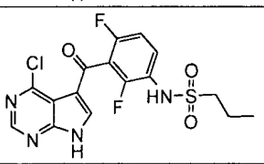
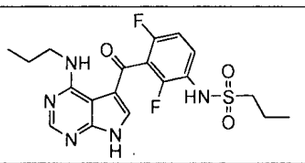
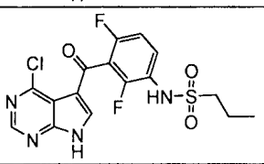
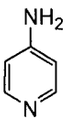
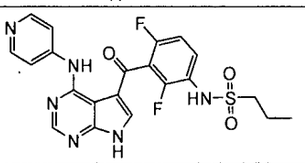
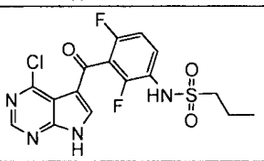
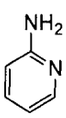
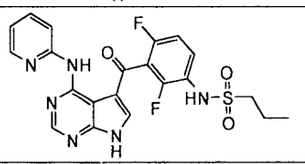
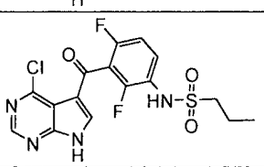
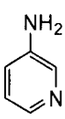
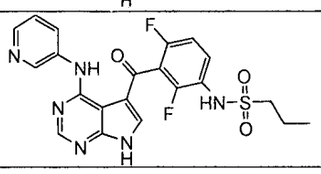
La siguiente tabla indica el compuesto 4-cloro-7H-pirrolo[2,3-d]pirimidina o 1H-pirrolo[2,3-b]piridina (columna 2) y compuesto de amina (columna 3) utilizado en la etapa 1 para ofrecer el compuesto deseado (columna 4). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 5.

Número de comp.	7H-pirrolo[2,3-d]pirimidina	Estructura de amina	Estructura del compuesto	MS (ESI) $[M+H^+]^+$
P-1013				582.0
P-1020				554.0
P-1024				525.95
P-1026				512.0
P-1031		NH_3		497.9

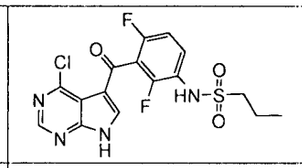
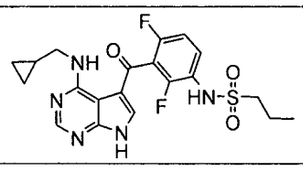
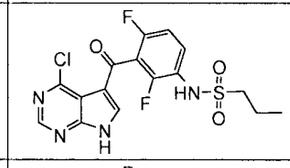
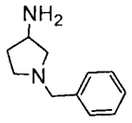
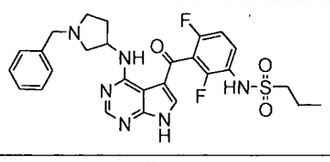
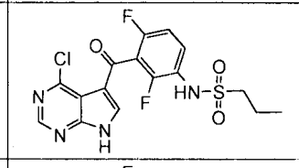
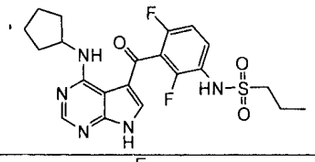
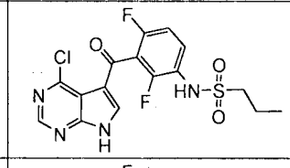
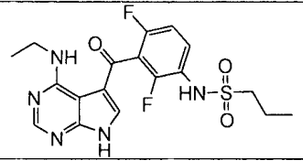
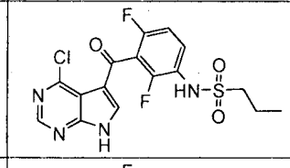
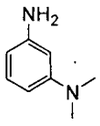
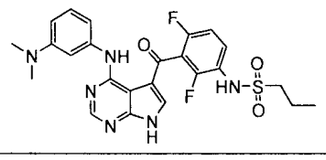
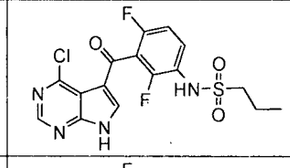
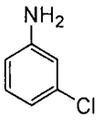
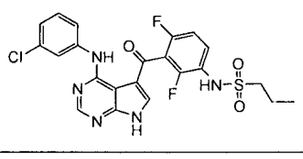
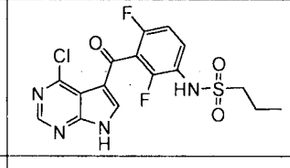
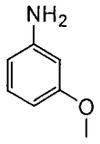
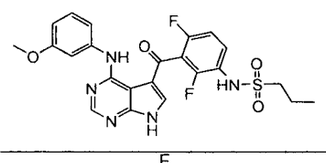
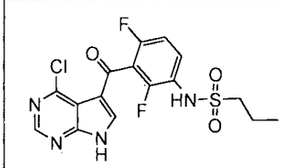
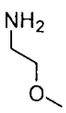
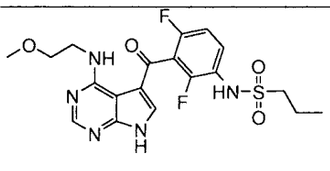
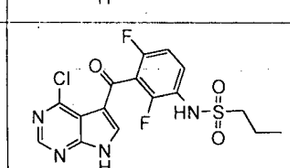
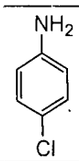
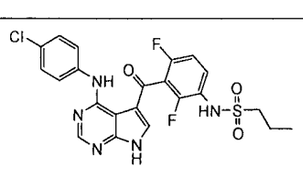
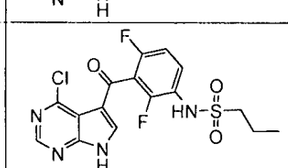
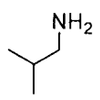
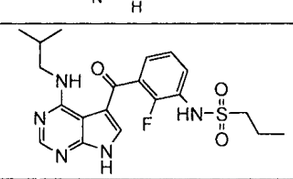
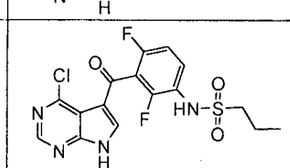
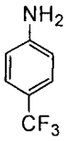
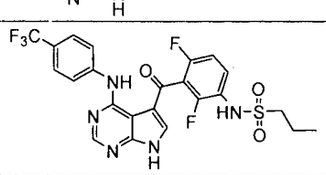
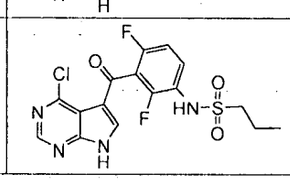
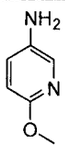
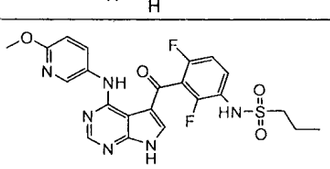
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P-1037				573.9
P-1039				540.0
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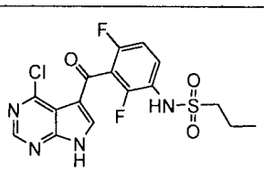
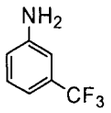
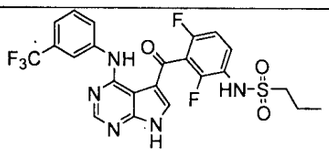
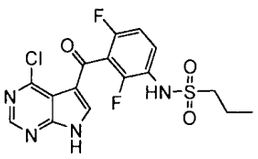
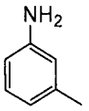
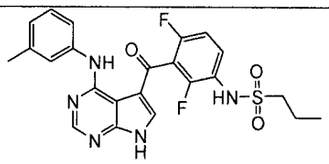
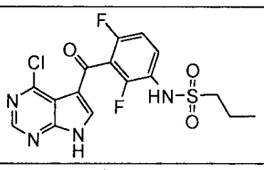
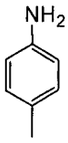
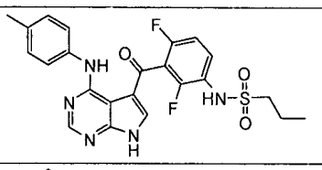
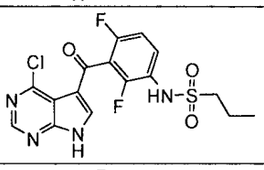
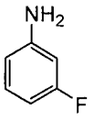
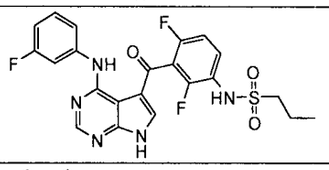
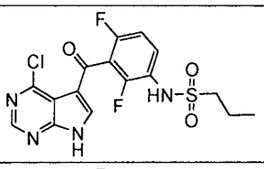
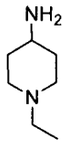
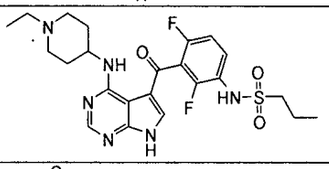
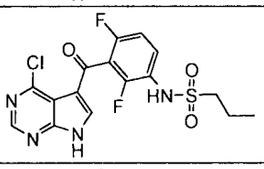
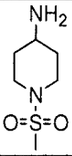
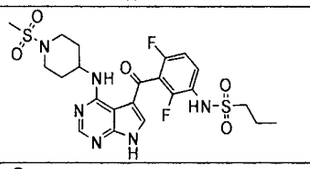
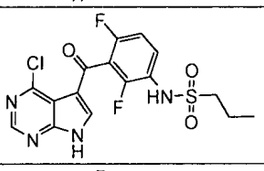
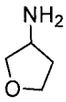
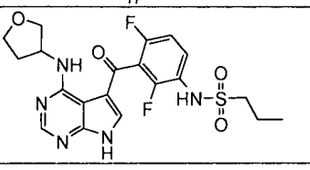
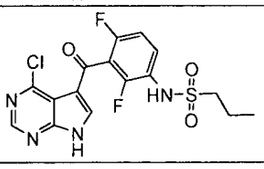
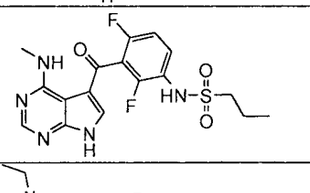
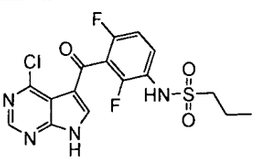
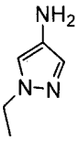
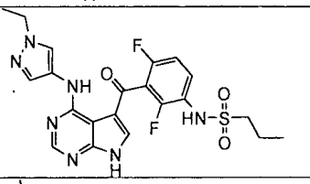
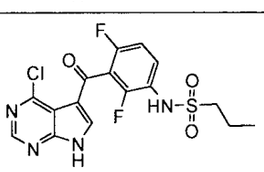
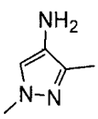
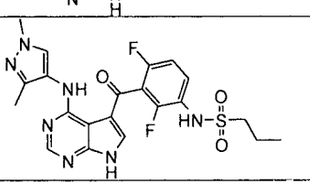
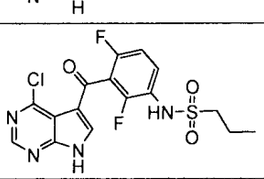
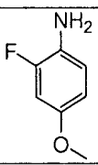
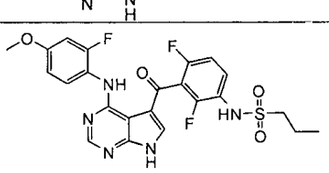
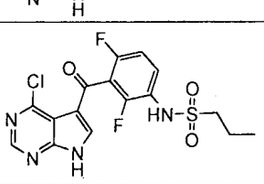
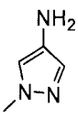
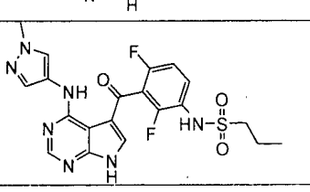
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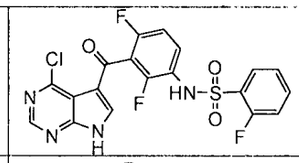
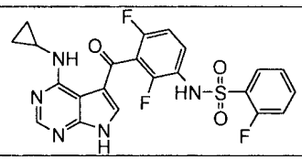
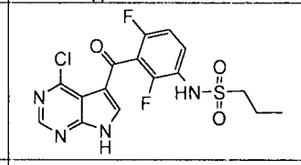
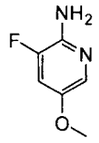
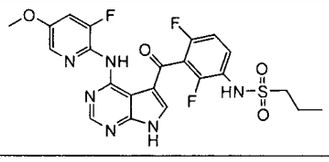
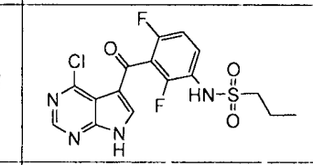
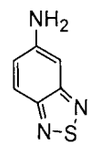
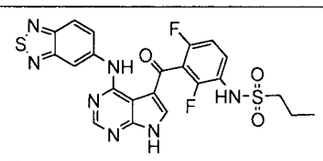
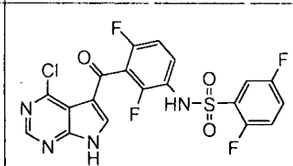
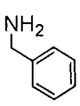
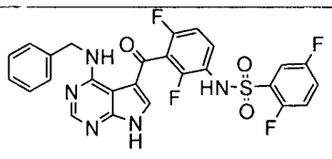
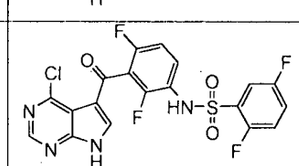
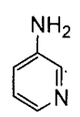
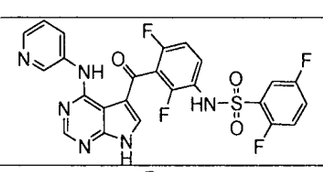
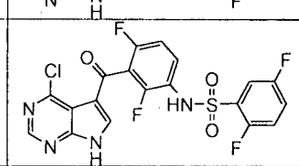
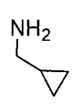
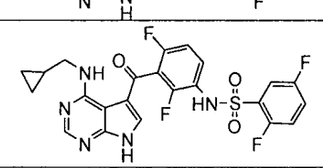
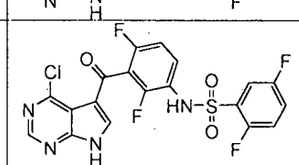
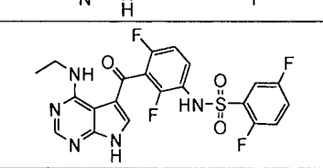
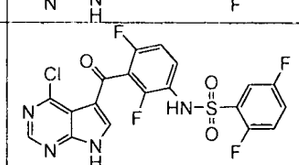
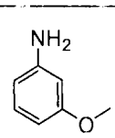
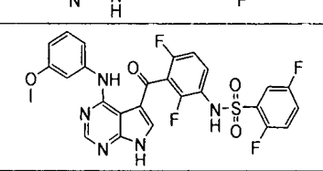
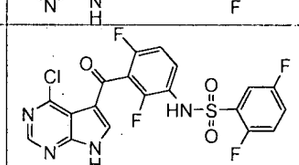
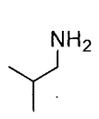
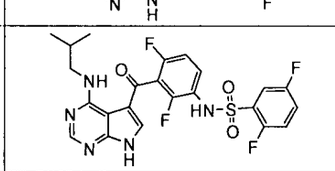
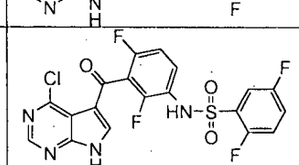
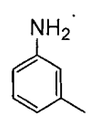
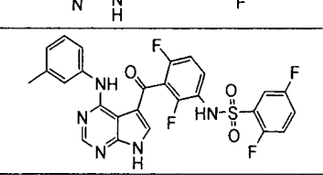
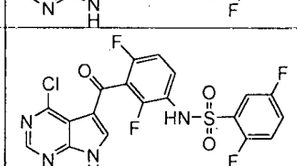
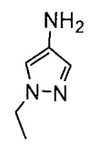
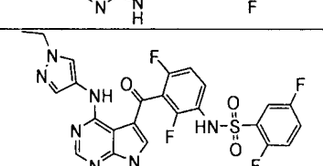
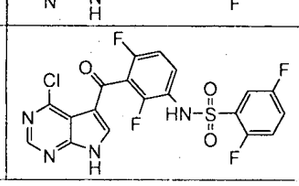
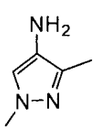
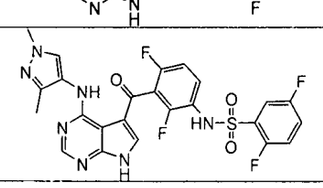
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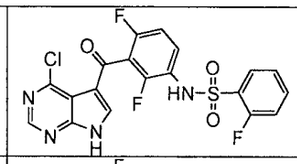
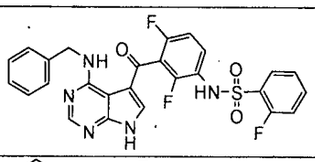
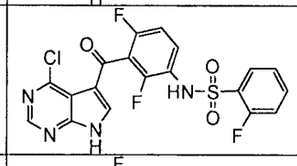
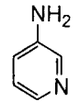
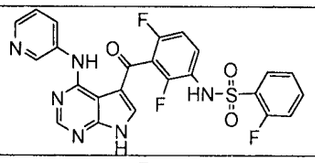
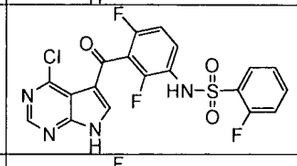
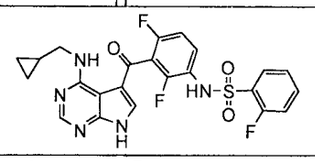
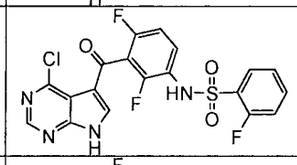
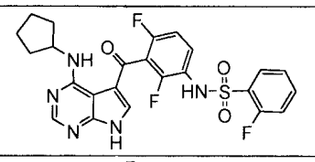
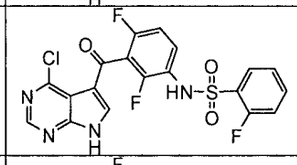
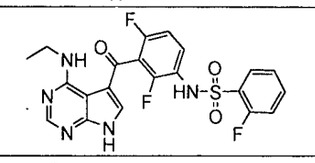
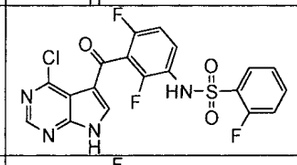
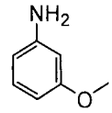
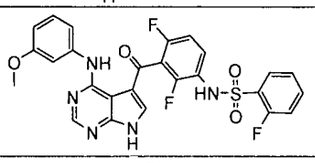
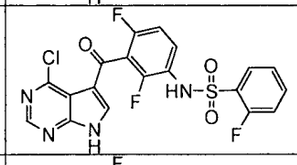
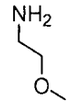
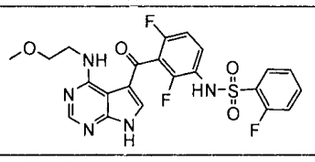
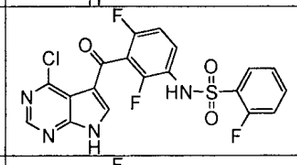
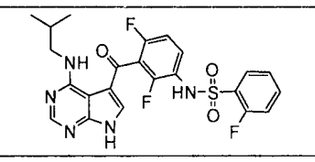
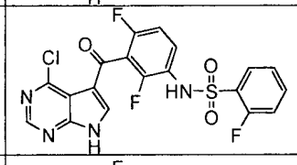
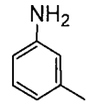
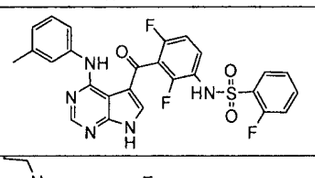
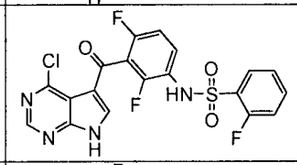
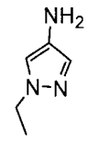
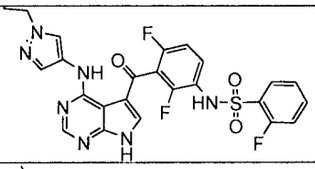
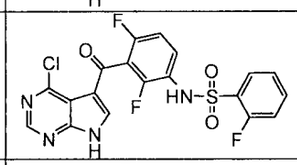
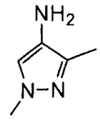
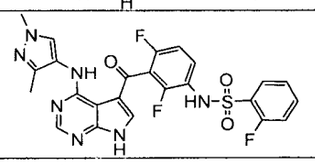
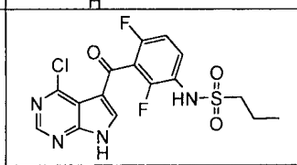
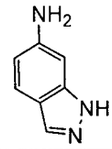
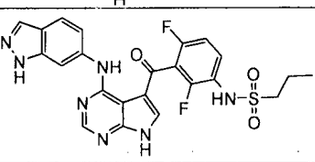
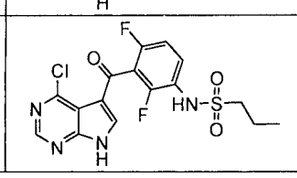
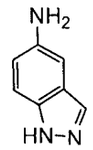
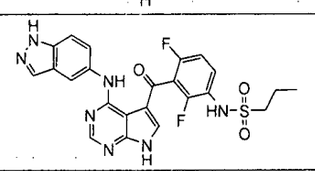
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P-1067				522.25
P-1068				513.9 $[M-H^+]^-$
P-1069				559.9
P-1072				522.0
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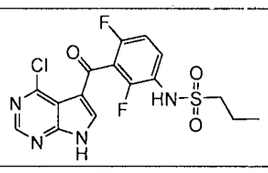
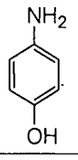
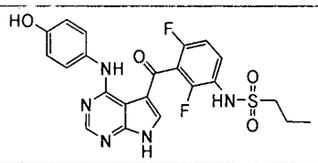
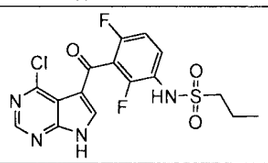
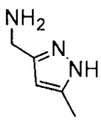
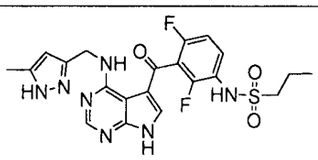
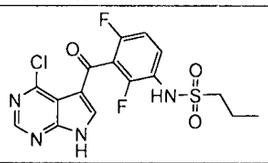
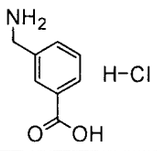
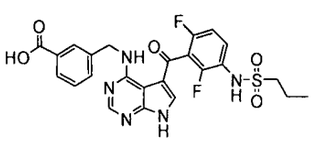
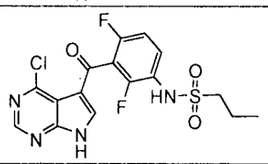
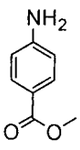
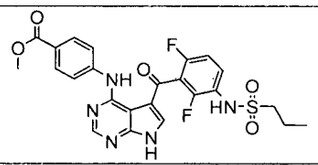
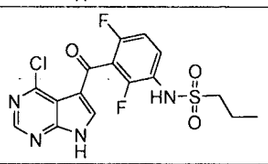
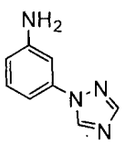
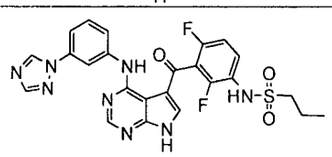
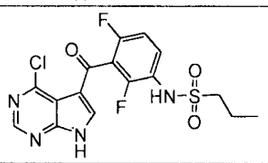
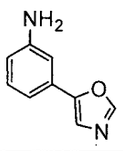
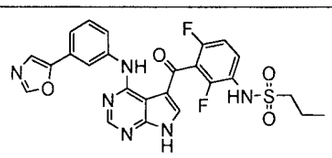
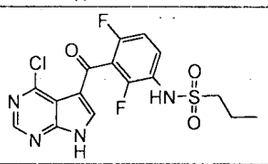
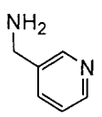
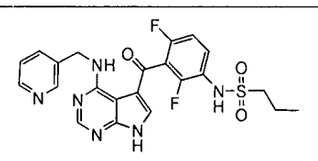
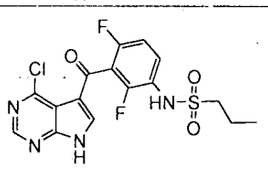
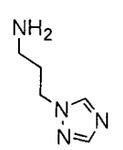
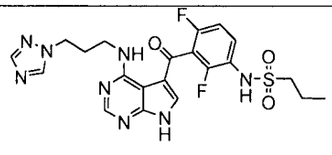
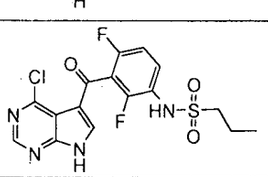
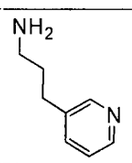
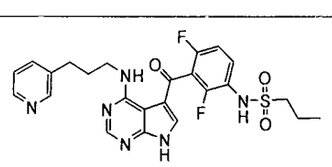
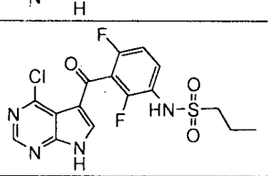
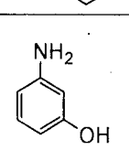
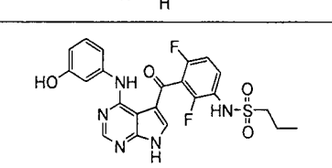
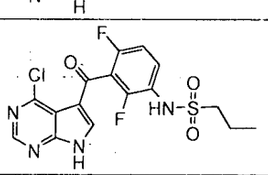
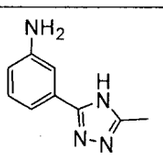
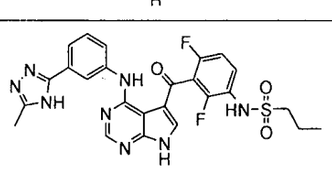
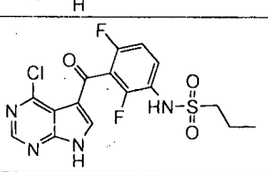
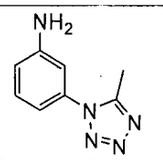
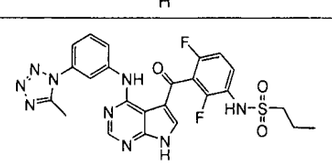
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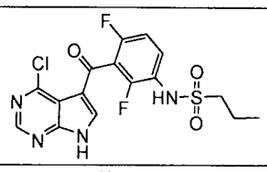
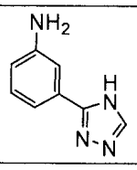
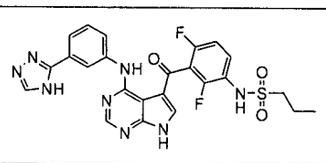
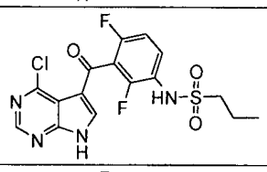
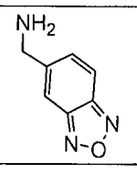
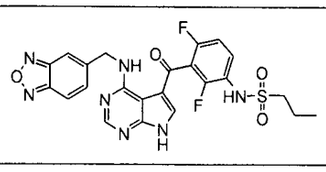
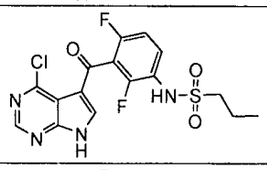
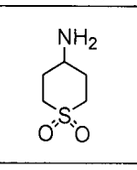
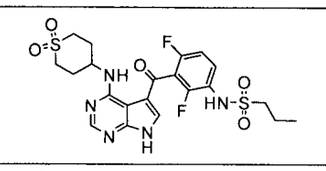
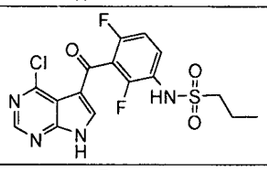
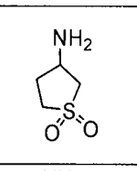
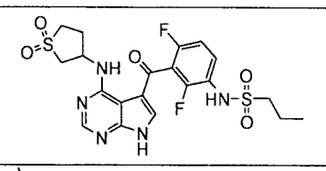
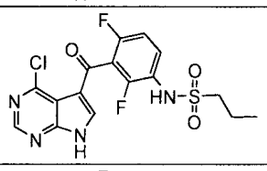
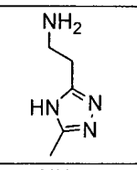
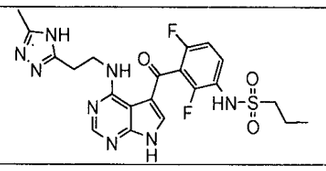
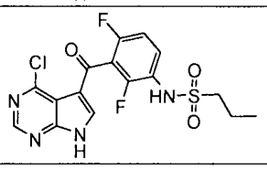
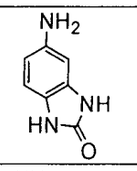
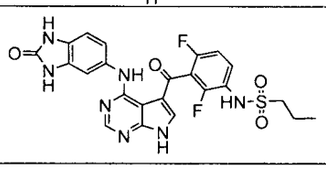
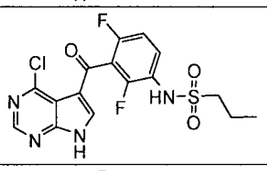
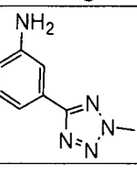
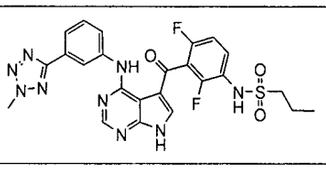
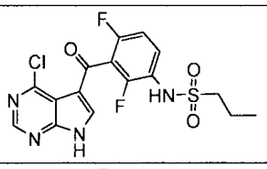
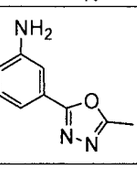
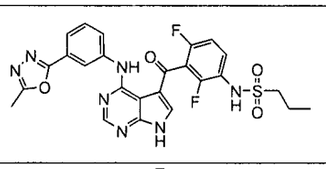
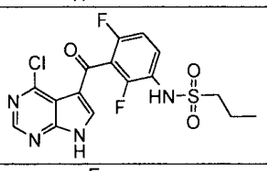
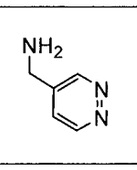
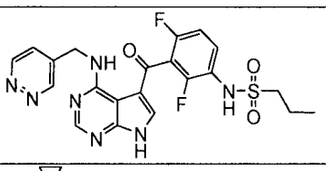
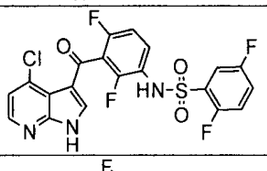
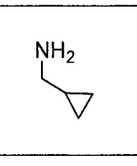
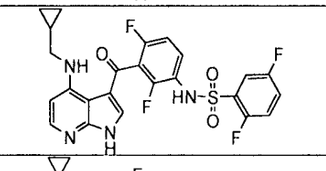
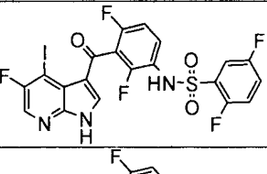
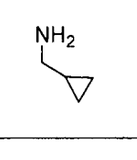
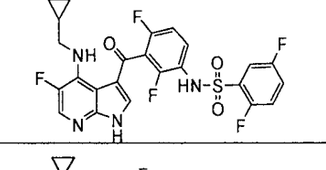
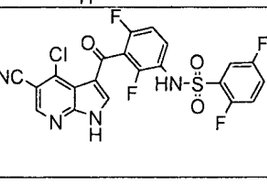
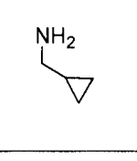
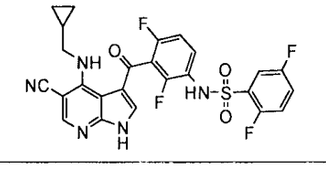
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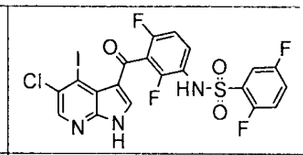
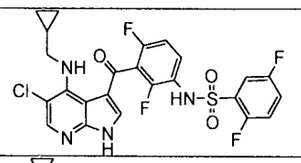
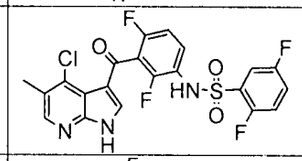
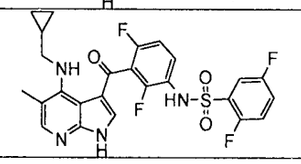
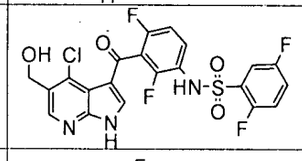
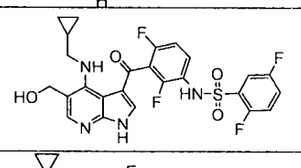
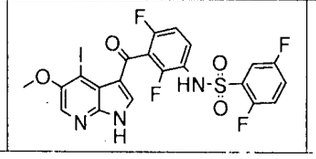
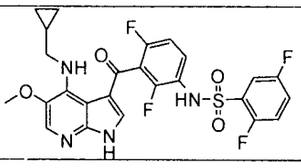
P-1103				488.0
P-1105				521.0
P-1134				530.0
P-1135				556.0
P-1136				543.5
P-1137				520.5
P-1138				494.0
P-1139				572.0
P-1140				522.0
P-1141				556.0
P-1142				560.0
P-1143				560.0

P-1144				538.5
P-1145				525.5
P-1146				502.0
P-1147				516.5
P-1148				476.0
P-1149				554.0
P-1150				506.0
P-1151				504.0
P-1152				538.5
P-1153				542.0
P-1154				542.0
P-1157				512.0
P-1158				512.0

P-1159				489.1
P-1160				488.0 $[M-H^+]^-$
P-1161				530.0
P-1162				530.0
P-1164				539.5
P-1165				539.5
P-1166				487.5
P-1167				505.0
P-1168				515.5
P-1169				488.0
P-1170				553.5
P-1171				554.0

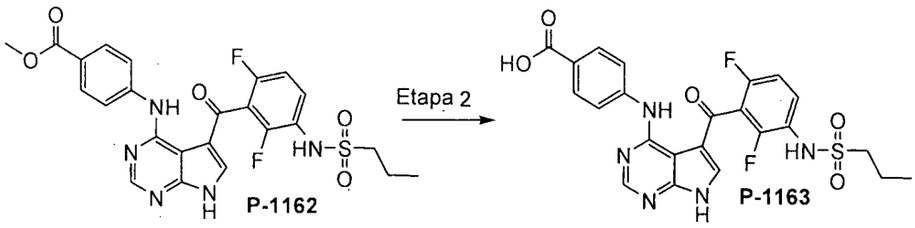
P-1172				539.5
P-1173				528.0
P-1174				528.0
P-1175				514.5
P-1176				505.0
P-1177				528.0
P-1178				554.0
P-1179				554.0
P-1180				488.0
P-2018*				
P-2019				535.1 $[M-H^+]^-$
P-2020				544.0 $[M-H^+]^-$

256

P-2021				
*P-2022**				
*P-2023**				
*P-2024**				

* Catalizador de paladio se utilizó para facilitar la reacción de acoplamiento.

[0273] El ácido 4-{5-[2,6-difluoro-3-(propano-1-sulfonilamino)-benzoil]-7H-pirrolo[2,3-d]pirimidin-4-ilamino}-benzoico **P-1163** se prepara a partir del metil éster de ácido 4-{5-[2,6-difluoro-3-(propano-1-sulfonilamino)-benzoil]-7H-pirrolo[2,3-d]pirimidin-4-ilamino}-benzoico **P-1162** por la siguiente Etapa 2.



*Etapa 2 - Preparación de ácido 4-{5-[2,6-difluoro-3-(propano-1-sulfonilamino)-benzoil]-7H-pirrolo[2,3-d]pirimidin-4-ilamino}-benzoico (**P-1163**):*

[0274] El metil éster de ácido 4-{5-[2,6-difluoro-3-(propano-1-sulfonilamino)-benzoil]-7H-pirrolo[2,3-d]pirimidin-4-ilamino}-benzoico (**P-1162**, 26 mg, 0.05 mmol) se combina con 1 ml de metanol, 0.5 ml de tetrahidrofurano, y 0.5 ml de hidróxido de sodio 2 M. La reacción se agita a temperatura ambiente durante 48 horas, entonces se neutraliza con ácido clorhídrico 1 M y los solventes volátiles se remueven bajo vacío. Al suspensión acuosa restante se filtra para recolectar los sólidos, los cuales se secan bajo vacío para proporcionar el compuesto deseado (**P-1163**, 25 mg). MS (ESI) $[M+H^+]^+ = 516.0$.

Ejemplo 9: Propiedades de los compuestos

[0275] Aunque la actividad inhibitoria de los compuestos en cualquier Raf cinasa es importante para su actividad para tratar la enfermedad, los compuestos descritos en este documento muestran propiedades favorables que proporcionan ventajas como farmacéuticos también. Además de demostrar la actividad inhibitoria de cinasas contra cualquiera o todas las B-Raf, c-Raf-1 y B-Raf V600E en ensayos bioquímico y basados en células, los compuestos pueden mostrar solubilidad favorable, propiedades farmacocinéticas favorables, y baja inhibición de Cyp. Los compuestos se valoran en los siguientes ensayos o ensayos similares disponibles para u experto en la técnica.

[0276] Ensayos para actividad bioquímica y basada en células se conocen en la técnica, por ejemplo, como se describe en la publicación de PCT WO 2007/002433, la descripción de la cual se incorpora por la presente para referencia dado que se relaciona con tales ensayos. Por ejemplo, los valores de actividad bioquímica IC_{50} se determinan con respecto a la inhibición de la actividad de cinasa B-Raf, actividad de cinasa c-Raf-1, o actividad de cinasa B-Raf V600E, donde la inhibición de la fosforilación de un sustrato peptídico se mide en función de la concentración del compuesto. Los compuestos a probar se diluyen en dimetil sulfóxido a una concentración de 0.1 mM. Estos se diluyen en serie 15 µl a 30 µl de dimetil sulfóxido siete veces en placas de 96 pozos para un total de 8 puntos de dilución, y para cada punto de dilución 1 µL se agrega a un pozo de una placa de ensayo. Las placas se preparan de tal modo que cada pozo en una placa de 384 pozos contenga 1 µl de compuesto en 10 µl de volumen con 0.1 ng de enzima Raf (es decir, cualquiera de B-Raf, c-Raf-1 o B-Raf V600E, Upstate Biotechnology, o preparadas por métodos conocidos por un experto en la técnica), 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 biotina-MEK1 como sustrato. La reacción se inicia con la adición de 10 µl de 200 µM ATP (es decir, final 100 µM ATP). Después de la incubación de la reacción de cinasas durante 45 minutos a temperatura ambiente, 5 µl/pozo de Stop Solution se agregan (25 mM Hepes pH 7.5, 100 mM EDTA, 0.01% BSA con cuentas donadoras (cuentas con Estreptavidina, Perkin Elmer), cuentas aceptoras (recubiertas con Proteína A, Perkin Elmer), y anticuerpo anti phosphor MEK1/2 (CellSignal), cada uno a concentración final de 10 µg/ml). Las palcas are incubado durante 3 horas a temperatura ambiente y se leen en un lector Envision (Perkin Elmer). La fosforilación de Mek1 resulta en la unión del anticuerpo anti-phosphor-MEK1/2 y la asociación de las cuentas de donador y aceptor de tal modo que la señal correlacione con la actividad de cinasa. La señal versus concentración de compuesto se usa para determinar la IC_{50}.

[0277] Los compuestos se valoran en una diversidad de ensayos basados en células. Por ejemplo líneas celulares humanas con mutación B-Raf V600E (melanoma A375, melanoma SKMEL3, y adenocarcinoma de colon COLO205), así como líneas celulares tumorigéncias con B-RAF de tipo silvestre (adenocarcinoma de colon SW620) o con mutaciones de Ras (melanoma SKMEL2 y melanoma IPC298) se utilizan en tales ensayos. Ensayos similares pueden utilizarse para valorar líneas celulares tumorigéncias adicionales con mutaciones de Ras, incluyendo, pero sin limitarse a, 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.

[0278] En el día 1, las células se cuentan, entonces se centrifugan en un tubo cónico durante 5 minutos a 1000 rpm. El sobrenadante se remueve y las células se re-suspenden como sigue:

SW620 (ATCC catálogo # CCL-27): resuspendidas en medio de Leibovitz L-15, 2 mM de L-glutamina, 10% de suero fetal bovino a 6 X 10^4 células/ml.

A375 (ATCC catálogo # CRL-1619): resuspendidas en medio de Eagle modificado de Dulbecco, 4 mM de L-glutamina, 4.5 g/l de D-glucosa, 10% de suero fetal bovino a 6 X 10^4 células/ml.

COLO205 (ATCC catálogo # CCL-222): resuspendidas en RPMI 1640, 2 mM de L-glutamina, 1.5 g/l de bicarbonato de sodio, 4.5 g/l de D-glucosa, 10 mM de HEPES, 1.0 mM de piruvato de sodio, 10% de suero fetal bovino a 6 X 10^4 células/ml.

SKMEL2 (ATCC catálogo # HTB-68): resuspendidas en medio esencial Minimum Eagle, 2 mM de L-glutamina, 1.5 g/l de bicarbonato de sodio, 0.1 mM de aminoácidos no esenciales, 1.0 mM de piruvato de sodio, 10% de suero fetal bovino a 6 X 10^4 células/ml.

SKMEL3 (ATCC catálogo # HTB-69): resuspendidas en medio de McCoy's 5A, 1.5 mM de L-glutamina, 15% de suero fetal bovino a 6 X 10^4 células/ml.

IPC298 (DSMZ catálogo # ACC 251): resuspendidas en RPMI 1640, 2 mM de L-glutamina, 10% de suero fetal bovino a 6 X 10^4 células/ml.

[0279] Las células se colocan en placas (50 µL) en cada pozo de una placa de 96 pozos (Corning 3610) y se incuban a 37 °C en 5% CO_2 durante la noche, las células se colocan en placas a una concentración final de células como sigue:

SW620: 5,000 células por pozo.

A375: 2,000 células por pozo.

COLO205: 2,000 células por pozo.

SKMEL2: 2,000 células por pozo.

SKMEL3: 3,000 células por pozo.

IPC298: 2,000 células por pozo.

[0280] En el día 2, el compuesto a una concentración máxima de 5 mM se diluye de manera seriada 1:3 para un total de 8 puntos de titulación con DMSO como control. Una alícuota de 1 µL de cada punto de dilución se agrega a 249 µL de medio de crecimiento y 50 µL se agrega a un pozo que contiene células, proporcionando 10 µM de compuesto para el punto de máxima concentración. Las células se incuban durante 3 días a 37 °C en 5% de CO_2.

[0281] En el día 5, el sistema ATPlite 1 step Luminescence Assay System (Perkin Elmer # 6016739) se lleva a temperatura ambiente en conjunto con los cultivos celulares. ATPlite se agrega en 25 µl a cada pozo, se agita durante 2 minutos, y las células se incuban a temperatura ambiente durante 10 minutos, entonces la luminiscencia se lee en un lector Safire. La luminiscencia medida se correlaciona directamente con el número de células, de tal modo que la lectura, como una función de la concentración del compuesto, se usa para determinar el valor de la IC_{50}.

[0282] Se entiende que los resultados de estos ensayos pueden variar dado que las condiciones de ensayo varían. Los niveles de inhibición determinados bajo las condiciones descritas en este documento representan una actividad relativa para los compuestos probados bajo las condiciones específicas empleadas. Es probable que los ensayos basados en células muestren variabilidad debido a la complejidad del sistema y la sensibilidad del mismo para cualquier cambio en las condiciones de ensayo. Como tal, cierto nivel de inhibición en los ensayos basados en células es indicativo de que los compuestos tienen cierta actividad inhibitoria para esas células, mientras que la falta de inhibición por debajo del umbral de la concentración más alta probada no necesariamente indica que el compuesto no tiene actividad inhibitoria sobre las células, solamente que, bajo las condiciones probadas, no se observa inhibición. Los resultados para los compuestos que se prueban y no muestran sustancialmente inhibición por debajo de la

concentración más alta probada se representan como "-" en las tablas. En algunos casos, los compuestos no se probaron en todos los ensayos, o los resultados de los ensayos no fueron válidos, como se indica por NA en las tablas.

[0283] La siguiente tabla proporciona datos que indican la actividad inhibitoria bioquímica de B-Raf, B-Raf V600E y c-Raf-1 y las relaciones correspondientes de actividad para compuestos ejemplares como se describe en este documento:

Número de compuesto	Actividad bioquímica (IC_{50} µM)			Relación de actividad bioquímica		
	B-Raf	V600E	c-Raf-1	B/C	V600E/C	B/V600E
P-1001	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1002	> 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1003	> 0.1	< 0.1	< 0.1	> 10	0.1-10	> 10
P-1004	> 0.1	< 0.1	< 0.1	> 10	0.1-10	> 10
P-1005	> 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1006	> 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1007	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1008	> 0.1	> 0.1	> 0.1	0.1-10	0.1-10	0.1-10
P-1009	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1010	> 0.1	> 0.1	> 0.1	0.1-10	> 10	0.1-10
P-1011	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1012	> 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1013	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1014	> 0.1	> 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1015	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1016	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1017	> 0.1	> 0.1	> 0.1	0.1-10	> 10	0.1-10
P-1018	> 0.1	> 0.1	> 0.1	> 10	0.1-10	> 10
P-1019	> 0.1	> 0.1	> 0.1	0.1-10	0.1-10	0.1-10
P-1020	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1021	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1022	> 0.1	> 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-1023	> 0.1	> 0.1	> 0.1	0.1-10	> 10	0.1-10
P-1024	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1025	> 0.1	> 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1026	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1027	> 0.1	> 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1028	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1029	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1030	> 0.1	> 0.1	< 0.1	0.1-10	> 10	< 0.1
P-1031	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1032	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-1033	> 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1034	> 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1035	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-1036	> 0.1	< 0.1	< 0.1	> 10	0.1-10	> 10
P-1037	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1038	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1039	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-1040	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1041	< 0.1	< 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-1042	< 0.1	< 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1043	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1044	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1045	> 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1046	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1047	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10

P-1048	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-1049	> 0.1	> 0.1	> 0.1	> 10	> 10	0.1-10
P-1050	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-1051	< 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1052	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-1053	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1054	< 0.1	< 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1055	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1056	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-1057	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1058	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1059	> 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-1060	< 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-1061	> 0.1	> 0.1	> 0.1	0.1-10	> 10	0.1-10
P-1062	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-1063	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-2001	< 0.1	< 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-2002	< 0.1	< 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-2003	< 0.1	< 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-2004	< 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-2005	< 0.1	< 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-2006	< 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-2007	< 0.1	< 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-2008	< 0.1	< 0.1	< 0.1	0.1-10	0.1-10	0.1-10
P-2009	< 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10
P-2010	< 0.1	< 0.1	< 0.1	> 10	> 10	0.1-10
P-2011	< 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-2012	> 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-2013	> 0.1	< 0.1	< 0.1	> 10	0.1-10	0.1-10
P-2014	> 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-2015	> 0.1	> 0.1	< 0.1	> 10	0.1-10	> 10
P-2016	> 0.1	> 0.1	< 0.1	0.1-10	> 10	0.1-10
P-2017	> 0.1	> 0.1	< 0.1	> 10	> 10	0.1-10

[0284] Como una indicación de la solubilidad relativa, se valoró la turbidez de los compuestos en soluciones acuosas. Para valorar posibles propiedades del compuesto en diferentes compartimientos fisiológicos, tal como estómago, intestino y sangre, se usó una serie de reguladores acuosos con pH variable. De esta manera, cada compuesto se diluye en cuatro diferentes reguladores fisiológicamente relevantes y la turbidez de la solución se mide por espectrofotometría. La concentración de compuesto que demuestra turbidez al formar suficiente suspensión insoluble para elevar la densidad óptica promedio por arriba de 0.01 en tres longitudes de onda (490, 535, y 650 nm), se usa para definir el límite de solubilidad del compuesto en ese regulador.

[0285] Los compuestos se disuelven a una concentración de 25 mM en dimetilsulfóxido, entonces se diluyen en serie 1:1 en una placa de 96 pozos, diluyendo 10 veces en dimetilsulfóxido puro, con el pozo final de cada hilera siendo un dimetilsulfóxido solo. En una placa de ensayo, 99 µL de regulador apropiado se agregan a cada pozo, y 1 µL de cada dilución de muestra se agrega al regulador, alcanzando una diversidad de concentraciones totales finales en soluciones acuosas que tienen diferente pH. Los reguladores usados son Fluido Gástrico Simulado (SGF-pH 1.5) 0.5M NaCl, pH 1.5; Fluido Intestinal Simulado (SIF-pH 4.5 y pH 6.8) 0.05M NaH_2PO_4, pH 4.5 y 6.8; y Regulador Hepes (HEPES-pH 7.4) 10 mM HEPES, 150 mM NaCl, pH 7.4. Los compuestos control pireno, estriol y propranolol HCl también se

valoran. Las placas se centrifugaron y entonces se mezclaron durante 1 minuto, y la absorbancia se leyó usando un Tecan Safire II para leer longitudes de onda en el intervalo visible (490, 535, y 650 nm) en cuatro ubicaciones por pozo, reflejando el grado de turbidez presente. La densidad óptica promedio para cada longitud de onda en cada pozo se graficó vs. concentración de compuesto, y la concentración en la que la curva cruza un umbral O.D. de 0.01 para cada longitud de onda se reportó como el resultado del ensayo de turbidez de punto final. El promedio de las tres longitudes de onda se usa para comparar turbidez de compuestos. Se considera que los compuestos tienen baja solubilidad si la concentración umbral es <31.3 μM, solubilidad moderada si la concentración umbral es 31.3 μM a 250 μM, y alta solubilidad si la concentración umbral es >250 μM.

[0286] La siguiente tabla indica la solubilidad relativa (L = baja, M = moderada, H = alta) con base en la concentración del umbral de turbidez a cada pH para compuestos ejemplares de acuerdo con la invención como se indica:

Número de compuesto	**umbral de turbidez** (L, M, H)			
	1.4	4.5	6.8	7.4
P-1001	H	M	M	M
P-1002	H	H	H	H
P-1003	H	M	M	M
P-1004	H	H	H	H
P-1005	H	L	L	L
P-1006	L	L	L	H
P-1007	L	L	L	L
P-1008	M	M	L	M
P-1009	H	L	L	M
P-1010	L	L	L	M
P-1011	M	L	L	L
P-1012	M	M	H	H
P-1013	L	L	L	M
P-1014	M		M	M
P-1016	L		L	H
P-1020	H			H
P-1024	M	L	L	L
P-1025	M	L	M	
P-1026			M	M
P-1027		L	M	
P-1028	M	L	L	M
P-1029	M			M
P-1030		M		M
P-1031	M	M	M	M
P-1032	L	L		
P-1033	H	H	H	H
P-1034	M	M	M	M
P-1035	L	L	L	L
P-1037	L	L	L	L
P-1039	M	M	M	M
P-1040	M	L	L	L
P-1041	H	M	M	M
P-1042	M	L	L	L
P-1043	H	M	M	M
P-1044	M	M	M	M
P-1045	M	L	L	L
P-1046	M	L	L	L
P-1047	M	L	L	L

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P-1048	M	M	M	M
P-1049	M	M	M	M
P-1050	H	M	M	M
P-1051	H	M	M	M
P-1052	L	L	L	L
P-1053	L	L	L	L
P-1054	M	L	L	L
P-1055	L	L	L	L
P-1056	M	L	L	L
P-1057	H	H	M	M
P-1058	M	L	L	L
P-1059	H	M	M	M
P-1060	H	M	H	H
P-1061	H	M	M	H
P-1062	L	L	L	L
P-1063	L	L	L	L
P-1073	M	L	L	L
P-1076	H	H	H	H
P-1077	H	L	L	L
P-1078	M	L	L	L
P-1079	M	L	L	L
P-1081	H	L	L	L
P-1084	M	M	M	M
P-1085	L	L	L	L
P-1087	M	L	M	M
P-1088	M	L	L	L
P-1094	L	L	M	L
P-1095	H	H	H	H
P-1099	M	L	M	M
P-1100	M	M	L	L
P-1101	L	L	L	L
P-1103	M	L	L	M
P-1104	H	M	M	M
P-1107	M	L	M	M
P-1143	L	L	L	L
P-1154	L	L	L	L
P-2001	M	M	M	M
P-2002	M	M	M	M
P-2003	M	M	M	M
P-2004	L	L	L	L
P-2005	M	L	L	M
P-2006	M	M	M	M
P-2007	M	M	M	M
P-2008	L	M	L	M
P-2009	L	M	M	M
P-2010	L	L	L	M
P-2011	L	L	L	L
P-2013	H	H	H	H
P-2014	L	L	L	L
P-2015	M	M	M	M
P-2016	L	L	L	M
P-2017	L	L	L	M

[0287] Las enzimas CYP (Citocromo P450) son las principales enzimas del metabolismo de fármacos presentes en el hígado. La inhibición de la actividad enzimática CYP (IC_{50}) para cada uno de CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4(BFC) y CYP3A4(BQ) se determina para los compuestos, donde

la inhibición del metabolismo de un sustrato conocido conduce a una disminución en la fluorescencia del producto metabolizado. La fluorescencia del producto se monitorea como una función de la concentración del compuesto.

[0288] Los compuestos se disuelven en dimetil sulfóxido a una concentración de 100 mM. Estos se diluyen 1 µl en 82 µl de acetonitrilo. Una alícuota de 11 µL de esta solución entonces se agrega a 204 µL de mezcla de cofactores (1.3% de sistema de Regeneración de NADPH Solución A, 1.04% de sistema de Regeneración de NADPH Solución B de BD Biosciences, 5% de acetonitrilo y 0.05% de DMSO). Estos entonces se diluyen de manera seriada 1:1 (160 µl a 160 µl de mezcla de cofactores) para un total de 10 puntos. Una alícuota de 10 µL de esta mezcla final se distribuye en placas de ensayo de 384 pozos y se incuba durante 10 minutos a 37 °C. Enzima y mezcla de sustratos (10 µL; 0.5 pmol CYP1A2/5 µM CEC; 1.0 pmol CYP2C9/75 µM MFC; 0.5 pmol CYP2C19/25 µM CEC; 1.5 pmol CYP2D6/1.5 µM AMMC; 1.0 pmol CYP3A4/50 µM BFC; o 1.0 pmol CYP3A4/40 µM BQ) se agrega a estas placas de ensayo. Las placas de ensayo se incuban a 37 °C (CYP1A2-15 min; CYP2C9-45 min; CYP2C19, 2D6 y 3A4-30 min) y se leen en un lector de placas Tecan Safire 2 (CYP1A2, 2C19 y 3A4 409 ex/460 em; CYP2C9 y 2D6 409 ex/530 em). La señal versus concentración de compuesto se usa para determinar la IC_{50}. Las enzimas y sustratos para este ensayo se obtienen de BD Biosciences. Aunque otros factores se implican en determinar los efectos de CYP in vivo, los compuestos preferentemente tienen valores de IC_{50} de >5 µM, más preferentemente valore de IC_{50} de > 10 µM.

[0289] La siguiente tabla indica la inhibición de Cyp para compuestos ejemplares de acuerdo con la invención como se indica:

Número de compuesto	Cyp IC_{50} (µM)					
	1A2	2C19	2C9	2D6	3A4(BFC)	3A4(BFC)
P-1001	> 10	> 10	> 10	> 10	< 5	> 10
P-1002	> 10	> 10	> 10	> 10	> 10	> 10
P-1003	> 10	> 10	5-10	> 10	> 10	5-10
P-1004	> 10	> 10	5-10	> 10	> 10	> 10
P-1005	> 10	5-10	> 10	> 10	5-10	> 10
P-1006	> 10	> 10	5-10	> 10	< 5	> 10
P-1007	> 10	> 10	> 10	> 10	5-10	5-10
P-1008	> 10	> 10	5-10	> 10	> 10	> 10
P-1009	> 10	5-10	< 5	> 10	< 5	> 10
P-1010	> 10	5-10	5-10	> 10	> 10	> 10
P-1011	> 10	5-10	> 10	> 10	< 5	> 10
P-1012	> 10	> 10	> 10	> 10	> 10	> 10
P-1013	> 10	> 10	> 10	> 10	> 10	> 10
P-1014	> 10	> 10	> 10	> 10	> 10	
P-1015	> 10	> 10	> 10	> 10	5-10	
P-1016	> 10	> 10	> 10	> 10	> 10	
P-1020	> 10	> 10	> 10	> 10	> 10	
P-1024	> 10	5-10	> 10	> 10	> 10	
P-1025	> 10	> 10	> 10	> 10	5-10	
P-1026	> 10	> 10	> 10	> 10	> 10	
P-1027	> 10	> 10	> 10	> 10	> 10	
P-1028	> 10	> 10	5-10	> 10	> 10	
P-1029	> 10	5-10	5-10	> 10	> 10	
P-1030	> 10	> 10	> 10	> 10	> 10	
P-1031	> 10	> 10	> 10	> 10	> 10	

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P-1032	> 10	5-10	> 10	> 10	> 10	
P-1033	> 10	> 10	> 10	> 10	> 10	
P-1034	> 10	5-10	> 10	> 10	5-10	
P-1035	> 10	5-10	> 10	> 10	5-10	
P-1037	> 10	< 5	> 10	> 10	> 10	
P-1038	> 10	5-10	5-10	> 10	5-10	
P-1039	> 10	> 10	> 10	> 10	5-10	
P-1040	> 10	> 10	> 10	> 10	5-10	> 10
P-1041	> 10	> 10	> 10	> 10	> 10	> 10
P-1042	> 10	5-10	> 10	> 10	> 10	> 10
P-1043	> 10	> 10	> 10	> 10	> 10	> 10
P-1044	> 10	< 5	> 10	> 10	> 10	> 10
P-1045	> 10	< 5	5-10	> 10	5-10	> 10
P-1046	> 10	> 10	> 10	> 10	> 10	> 10
P-1047	> 10	> 10	> 10	> 10	> 10	> 10
P-1048	> 10	> 10	> 10	> 10	> 10	> 10
P-1049	> 10	> 10	> 10	> 10	> 10	> 10
P-1050	> 10	> 10	> 10	> 10	> 10	> 10
P-1051	> 10	> 10	> 10	> 10	> 10	> 10
P-1052	> 10	< 5	< 5	> 10	5-10	> 10
P-1053	> 10	5-10	5-10	> 10	> 10	> 10
P-1054	> 10	> 10	5-10	> 10	> 10	> 10
P-1055	> 10	< 5	5-10	> 10	5-10	> 10
P-1056	> 10	> 10	> 10	> 10	> 10	> 10
P-1057	> 10	> 10	> 10	> 10	> 10	> 10
P-1058	> 10	> 10	> 10	> 10	5-10	> 10
P-1059	> 10	> 10	> 10	> 10	> 10	> 10
P-1060	> 10	> 10	> 10	> 10	> 10	> 10
P-1061	> 10	> 10	> 10	> 10	> 10	> 10
P-1062	> 10	> 10	< 5	> 10	5-10	5-10
P-1063	> 10	5-10	5-10	> 10	5-10	< 5
P-1073	> 10	> 10	> 10	> 10	> 10	> 10
P-1074	> 10	> 10	> 10	> 10	> 10	> 10
P-1077	> 10	> 10	> 10	> 10	> 10	> 10
P-1078	> 10	> 10	< 5	> 10	> 10	5-10
P-1079	> 10	> 10	> 10	> 10	> 10	> 10
P-1081	> 10	> 10	> 10	> 10	> 10	> 10
P-1090	> 10	> 10	> 10	> 10	> 10	> 10
P-1100	> 10	> 10	> 10	> 10	> 10	> 10
P-1101	> 10	> 10	> 10	> 10	> 10	> 10
P-1103	> 10	> 10	> 10	> 10	> 10	> 10
P-1104	> 10	> 10	> 10	> 10	> 10	> 10
P-1107	5-10	> 10	> 10	> 10	> 10	> 10
P-1111	> 10	> 10	5-10	> 10	> 10	> 10
P-1137	> 10	> 10	> 10	> 10	> 10	> 10
P-1139	> 10	> 10	> 10	> 10	> 10	> 10
P-1142	> 10	> 10	> 10	> 10	> 10	> 10
P-1149	> 10	> 10	> 10	> 10	> 10	> 10
P-1150	> 10	> 10	> 10	> 10	> 10	> 10
P-1153	> 10	> 10	> 10	> 10	> 10	> 10
P-1154	> 10	> 10	> 10	> 10	> 10	> 10
P-2001	> 10	5-10	> 10	> 10	> 10	> 10
P-2002	> 10	< 5	< 5	> 10	5-10	5-10
P-2003	> 10	> 10	< 5	> 10	5-10	5-10
P-2004	> 10	> 10	< 5	> 10	> 10	> 10
P-2005	> 10	> 10	< 5	> 10	> 10	> 10
P-2006	> 10	< 5	< 5	> 10	5-10	> 10
P-2007	> 10	> 10	< 5	> 10	> 10	> 10

P-2008	> 10	5-10	5-10	> 10	> 10	> 10
P-2009	> 10	> 10	> 10	> 10	> 10	> 10
P-2010	> 10	> 10	5-10	< 5	> 10	> 10
P-2011	> 10	< 5	> 10	5-10	> 10	> 10
P-2012	> 10	> 10	> 10	> 10	> 10	> 10
P-2013	> 10	> 10	> 10	> 10	5-10	> 10
P-2015	> 10	> 10	> 10	> 10	> 10	> 10

[0290] Las propiedades farmacocinéticas de los compuestos (incluyendo cualquier forma sólida o formulaciones de los mismos) se valoran en ratas Sprague Dawley machos o perros Beagle machos. Las ratas se dosificaron diariamente con un compuesto por inyecciones IV mediante catéteres yugulares implantados quirúrgicamente o por alimentación oral (PO). Cada compuesto se preparó como una solución de reserva de 20 mg/ml en dimetilsulfóxido, que además se diluyó para proporcionar la reserva de dosificación a la concentración deseada para las formulaciones IV o PO. Para dosificación IV, la reserva de dosificación se diluyó en una mezcla 1:1:8 de Solutol ®:etanol:agua. Para dosificación PO, la reserva de dosificación se diluyó en 1% de metilcelulosa. En un formato de casete (o cada compuesto, forma sólida del mismo o formulación del mismo se hace individualmente), los compuestos se diluyen a 0.5 mg/ml cada uno para dosificación IV y 0.4 mg/ml cada uno para dosificación PO y se dosificaron a 1 mg/kg (2 ml/kg) o 2 mg/kg (5 ml/kg), respectivamente. Para animales dosificados IV, se recolectaron muestras de sangre de vena caudal con anticoagulante de heparina de litio a 5, 15, 30, y 60 minutos y 4, 8, y 24 horas post dosificación cada día. Para animales dosificados PO, se recolectaron muestras de sangre de vena caudal con anticoagulante de heparina de litio a 30 minutos, 1, 2, 4, 8 y 24 horas post dosificación cada día. Los perros se dosifican diariamente por cápsulas orales en una formulación adecuada a 50 mg/ml. Se recolectaron muestras de sangre de vena cefálica con anticoagulante de heparina de litio a 30 minutos, 1, 2, 4, 8 y 24 horas post dosificación cada día. Todas las muestras se procesan a plasma y se congelan para análisis posterior de cada compuesto por LC/MS/MS. Los niveles plasmáticos en función del tiempo se grafican para valorar el AUC (ng*h/ml). Los compuestos de acuerdo con la presente invención preferentemente muestran propiedades farmacocinéticas mejoradas en relación con compuestos previamente descritos, es decir, tienen valores sustancialmente superiores para uno o más de AUC, Cmax y vida media en relación con los compuestos previamente descritos.

Ejemplo 10: Eficacia de los Compuestos en Combinación con Agentes Quimioterapéuticos de Referencia en cuatro líneas de células cancerosas humanas.

[0291] Los compuestos de la invención, tales como los compuestos de la Fórmula I, en combinación con un agente quimioterapéutico estándar, tal como 5-fluorouracilo, carboplatina, dacarbazina, gefitinib, oxaliplatina, paclitaxel, SN-38, temozolomida, o vinblastina, pueden valorarse para su efectividad en eliminar células tumorales humanas. Tales ensayos se conocen en la técnica, por ejemplo, como se describe en la solicitud de patente de E.U. número de serie 11/473,347, la descripción de la cual se incorpora por la presente para referencia dado que se relaciona con tales ensayos.

[0292] Atributos adicionales del complejo pueden usarse para demostrar las propiedades mejoradas, tales como comparación de la tasa de disolución intrínseca de un complejo de citrato sustancialmente amorfo

preparado de manera similar o formulación del mismo as en comparación con aquel de una forma cristalina del compuesto o formulación similar del mismo en fluido gástrico simulado (SGF) sin enzima y en fluido intestinal simulado (SIF). **Una gránulo de la muestra de prueba se disuelve en el fluido apropiado, y la absorbancia de luz UV como una función del tiempo se mide a 254 nm (SGF) o 310 nm (SIF) y se grafica.**

[0293] Todas las patentes y otras referencias citadas en la especificación son indicativas del nivel de habilidad de los expertos en la técnica a la cual pertenece la invención, y se incorporan para referencia en sus totalidades, incluyendo cualesquier tablas y figuras, en la misma magnitud como si cada referencia se hubiera incorporado para referencia en su totalidad individualmente.

[0294] Un experto en la técnica puede apreciar fácilmente que la presente invención se adapta bien para obtener los fines y ventajas mencionadas, así como aquellas inherentes a ello. Los métodos, variaciones, y composiciones descritas en este documento, como actualmente representativas de las modalidades preferidas, son ejemplares y no pretenden ser limitaciones en el alcance de la invención. Los cambios en ello y otros usos que se les ocurrirán a los expertos en la técnica, que se abarcan dentro del espíritu de la invención, se definen por el alcance de las reivindicaciones.

[0295] La invención ilustrativamente descrita en este documento de manera favorable puede practicarse en ausencia de cualquier elemento o elementos, limitación o limitaciones que no se describen específicamente en este documento. De esta manera, por ejemplo, en cada caso en este documento cualquiera de los términos "que comprende", "que consiste esencialmente de" y "que consiste de" puede reemplazarse con cualquiera de los otros dos términos. De esta manera, para una modalidad de la invención usando uno de los términos, la invención también incluye otra modalidad en donde uno de estos términos se reemplaza con otro de estos términos. En cada modalidad, los términos tienen su significado establecido. De esta manera, por ejemplo, una modalidad puede abarcar un método "que comprende" una serie de etapas, otra modalidad puede abarcar un método "que consiste esencialmente de" las mismas etapas, y una tercera modalidad puede abarcar un método "que consiste de" las mismas etapas. Los términos y expresiones que se han empleado se usan como términos de descripción y no de limitación, y no hay intención que en el uso de tales términos y expresiones se excluya cualesquier equivalentes de los atributos mostrados y descritos o porciones de los mismos, pero se reconoce que diversas modificaciones son posibles dentro del alcance de la invención reclamada. De esta manera, debe entenderse que, aunque la presente invención se ha descrito específicamente por modalidades preferidas y atributos opcionales, la modificación y variación de los conceptos descritos en este documento puede reordenarse por los expertos en la técnica, y que tales modificaciones y variaciones se consideran dentro del alcance de esta invención como se define por las reivindicaciones adjuntas.

[0296] Además, donde los atributos o aspectos de la invención se describan en cuanto a grupos de Markush u otra agrupación de alternativas, los expertos en la técnica reconocerán que la invención también se describe en consecuencia en cuanto a cualquier miembro individual o subgrupo de miembros del grupo de Markush u otro grupo.

[0297] También, a menos que se indique lo contrario, donde diversos valores numéricos se proporcionan para las modalidades, las modalidades adicionales se describen al tomar cualesquier 2 valores diferentes como los puntos finales de un intervalo. Tales intervalos están también dentro del alcance de la invención descrita.

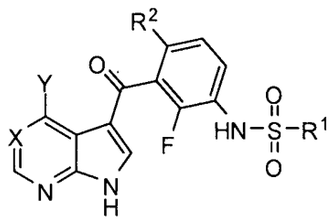
[0298] De esta manera, las modalidades adicionales están dentro del alcance de la invención y dentro de las siguientes reivindicaciones.

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REIVINDICACIONES

Lo que se reclama es:

1. Un compuesto que tiene la estructura química de la Fórmula I,



Fórmula I

o una sal, hidrato o solvato farmacéuticamente aceptable del mismo,

en donde:

X es –N= o –C(R^5)=;

Y se selecciona del grupo que consiste en flúor, cloro, bromo, yodo, alquilo inferior, alcoxi inferior, haloalquilo, CN, -OH, cicloalquilo, -OR^8, y –N(R^3)(R^4); en donde:

R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en (i) hidrógeno, -OR^8 y alquilo inferior opcionalmente sustituido con uno o más R^{11}; (ii) cicloalquilo o cicloalquilalquilo, cada uno de los cuales se sustituye opcionalmente con uno o más R^{12}; (iii) heterocicloalquilo o heterocicloalquilalquilo, cada uno de los cuales se sustituye opcionalmente con uno o más R^{13}; (iv) arilo o arilalquilo, cada uno de los cuales se sustituye opcionalmente con uno o más R^{14}, opcionalmente, en donde los dos grupos R^{14} adyacente en el anillo arilo se toman en conjunto para formar un anillo aromático hetero cíclico de 5 o 6 miembros que tiene de 1-4 heteroátomos seleccionados de O o N; y (v) heteroarilo o heteroarilalquilo, cada uno de los cuales se sustituye opcionalmente con uno o más R^{15}; o

R^3 y R^4 son alquilo inferior; o

R^3 y R^4 se combinan con el átomo de nitrógeno al cual se unen para formar un anillo de 3-7 miembros que tiene 0-1 heteroátomo de anillo adicional seleccionado de O, N o S, en donde el átomo de nitrógeno o azufre se oxida opcionalmente;

R^1 se selecciona del grupo que consiste en alquilo inferior, haloalquilo, haloalcoxi, alquilo inferior sustituido con flúor, cicloalquilo opcionalmente sustituido con uno o más R^7, heterocicloalquilo, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, arilo opcionalmente sustituido con uno o más R^6 y heteroarilo opcionalmente sustituido con uno o más R^7;

R2 es hidrógeno, flúor, cloro o alquilo inferior opcionalmente sustituido con uno o más flúor;

R^5 se selecciona del grupo que consiste en hidrógeno, flúor, cloro, -CN, alquilo inferior opcionalmente sustituido con uno o más R^{16}, y alcoxi inferior opcionalmente sustituido con uno o más R^{17};

cada R^6, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, cloro, -CN, -NO_2, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, -C(O)-O-R^{15}, -N(H)-C(O)-R^{16}, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior; o dos R^5 en carbonos adyacentes se combinan para formar un heterocicloalquilo fusionado opcionalmente sustituido con uno o más alquilo inferior;

cada R^7, cuando se presenta, se selecciona independientemente del grupo que consiste en alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, -C(O)-O-R^{20}, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior;

R^8 es hidrógeno, alquilo inferior opcionalmente sustituido con uno o más flúor, o, cuando R^8 es un alquilo C_{2-6}, el alquilo opcionalmente puede sustituirse con uno o más R^{21}; cicloalquilo opcionalmente sustituido con uno o más R^{21}, o heterocicloalquilo opcionalmente sustituido con uno o más R^{21};

cada R^{11}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, cicloalquilo opcionalmente sustituido con uno o más R^{12}, heterocicloalquilo opcionalmente sustituido con uno o más R^{13}, arilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo opcionalmente sustituido con uno o más R^{15};

cada R^{12}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, -N(H)-C(O)-R^{22}, -N(H)-$S(O)_2$-R^{23}, C(O)-R^{24}, y $S(O)_2$-R^{25};

cada R^{13}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, -N(H)-C(O)-R^{26}, -N(H)-$S(O)_2$-R^{27}, C(O)-R^{28}, $S(O)_2$-R^{29}, y alquilo inferior opcionalmente sustituido con uno o más R^{30};

cada R^{14} y R^{15}, cuando se presenta, se seleccionan independientemente del grupo que consiste en flúor, cloro, -OH, -NH_2, -CN, -NO_2, -N(H)-C(O)-R^{31}, -N(H)-$S(O)_2$-R^{32}, C(O)-R^{33}, $S(O)_2$-R^{34}, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, arilo opcionalmente sustituido con uno o más R^{35}, y heteroarilo opcionalmente sustituido con uno o más R^{36};

cada R16, cuando se presenta, es independientemente flúor, -OH, alcoxi inferior, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R17, cuando se presenta, es independientemente flúor, -OH, alcoxi inferior, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{18} y R^{20}, cuando se presentan, son independientemente hidrógeno, alquilo inferior, o alquilo inferior sustituido con flúor;

cada R^{19}, R^{22}, R^{23}, R^{26}, R^{27}, R^{31} y R^{32}, cuando se presentan, son independientemente alquilo inferior o alquilo inferior sustituido con flúor;

cada R^{21}, cuando se presenta, es flúor, -OH, alcoxi inferior, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{24}, R^{25}, R^{28}, R^{29}, R^{33}, y R^{34}, cuando se presentan, son independientemente alquilo inferior, alquilo inferior sustituido con flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, -NH_2, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{30}, cuando se presenta, es independientemente flúor, arilo opcionalmente sustituido con uno o más R^{35} o heteroarilo opcionalmente sustituido con uno o más R^{36}; y

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cada R^{35} y R^{36}, cuando se presentan, se seleccionan independientemente del grupo que consiste en flúor, cloro, -OH, $-NH_2$, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino.

2. El compuesto de conformidad con la reivindicación 1, en donde:

X es -N= o $-C(R^5)=$; en donde R^5 se selecciona del grupo que consiste en hidrógeno, flúor, cloro, -CN, alquilo inferior y alcoxi inferior, en donde el alquilo inferior o alcoxi inferior se sustituye opcionalmente con de uno a tres grupos seleccionados de flúor, -OH, alcoxi inferior, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

Y se selecciona del grupo que consiste en flúor, cloro, bromo, yodo, alquilo inferior, alcoxi inferior, haloalquilo, CN, -OH, cicloalquilo, $-OR^8$, y $-N(R^3)(R^4)$; en donde:

R^3 es hidrógeno y R^4 se selecciona del grupo que consiste en (i) hidrógeno, $-OR^8$ y alquilo inferior opcionalmente sustituido con de uno a tres R^{11}; (ii) cicloalquilo o cicloalquilalquilo, cada uno de los cuales se sustituye opcionalmente con de uno a tres R^{12}; (iii) heterocicloalquilo o heterocicloalquilalquilo, cada uno de los cuales se sustituye opcionalmente con de uno a tres R^{13}; (iv) arilo o arilalquilo, cada uno de los cuales se sustituye opcionalmente con de uno a tres R^{14} opcionalmente, en donde los dos grupos R^{14} adyacentes en el anillo arilo se toman en conjunto para formar un anillo aromático heterocíclico de 5 o 6 miembros que tiene de 1-4 heteroátomos seleccionados de O o N; y (v) heteroarilo o heteroarilalquilo, cada uno de los cuales se sustituye opcionalmente con de uno a tres R^{15}; o

R^3 y R^4 son alquilo inferior; o

R^3 y R^4 se combinan con el átomo de nitrógeno al cual se unen para formar un anillo de tres a siete miembros que tiene 0-1 heteroátomo de anillo adicional seleccionado de O, N o S, en donde el átomo de nitrógeno o azufre se oxida opcionalmente;

R^1 se selecciona del grupo que consiste en alquilo inferior, haloalquilo, haloalcoxi, alquilo inferior sustituido con flúor, cicloalquilo opcionalmente sustituido con uno a tres R^7, heterocicloalquilo, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, arilo opcionalmente sustituido con uno a tres R^6 y heteroarilo opcionalmente sustituido con uno a tres R^7;

R^2 es hidrógeno, flúor, cloro, o alquilo inferior opcionalmente sustituido con de uno a cinco átomos de flúor;

cada R^6, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, cloro, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, $-C(O)-O-R^{15}$, $-N(H)-C(O)-R^{16}$, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior; o dos R^5 en carbonos adyacentes se combinan para formar un heterocicloalquilo fusionado opcionalmente sustituido con uno o más alquilo inferior;

cada R^7, cuando se presenta, se selecciona independientemente del grupo que consiste en alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, $-C(O)-O-R^{20}$, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior;

R^8 es hidrógeno, alquilo inferior opcionalmente sustituido con uno o más flúor, o, cuando R^8 es un alquilo C_{2-6}, el alquilo opcionalmente puede sustituirse con uno o más R^{21}; cicloalquilo opcionalmente sustituido con uno o más R^{21}, o heterocicloalquilo opcionalmente sustituido con uno o más R^{21};

cada R^{11}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, cicloalquilo opcionalmente sustituido con uno o más R^{12}, heterocicloalquilo opcionalmente sustituido con uno o más R^{13}, arilo opcionalmente sustituido con uno o más R^{14}, y heteroarilo opcionalmente sustituido con uno o más R^{15};

cada R^{12}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, alquilo inferior, alquilo inferior sustituido con flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, $-N(H)-C(O)-R^{22}$, $-N(H)-S(O)_2-R^{23}$, $C(O)-R^{24}$, y $S(O)_2-R^{25}$;

cada R^{13}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, $-N(H)-C(O)-R^{26}$, $-N(H)-S(O)_2-R^{27}$, $C(O)-R^{28}$, $S(O)_2-R^{29}$, y alquilo inferior opcionalmente sustituido con uno o más R^{30};

cada R^{14} y R^{15}, cuando se presenta, se seleccionan independientemente del grupo que consiste en flúor, cloro, -OH, $-NH_2$, -CN, $-NO_2$, $-N(H)-C(O)-R^{31}$, $-N(H)-S(O)_2-R^{32}$, $C(O)-R^{33}$, $S(O)_2-R^{34}$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, arilo opcionalmente sustituido con uno a tres R^{35}, y heteroarilo opcionalmente sustituido con uno a tres R^{36};

cada R^{18} y R^{20}, cuando se presentan, son independientemente hidrógeno, alquilo inferior, o alquilo inferior sustituido con flúor;

cada R^{19}, R^{22}, R^{23}, R^{26}, R^{27}, R^{31} y R^{32}, cuando se presentan, son independientemente alquilo inferior o alquilo inferior sustituido con flúor;

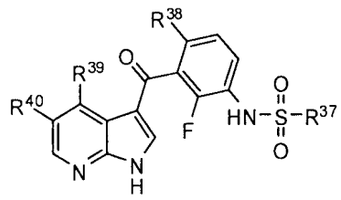
cada R^{21}, cuando se presenta, es flúor, -OH, alcoxi inferior, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{24}, R^{25}, R^{28}, R^{29}, R^{33}, y R^{34}, cuando se presentan, son independientemente alquilo inferior, alquilo inferior sustituido con flúor, -OH, alcoxi inferior, alcoxi inferior sustituido con flúor, $-NH_2$, mono-alquilamino, di-alquilamino, cicloalquilamino, o heterocicloalquilamino;

cada R^{30}, cuando se presenta, es independientemente flúor, arilo opcionalmente sustituido con uno o más R^{35} o heteroarilo opcionalmente sustituido con uno a tres R^{36}; y

cada R^{35} y R^{36}, cuando se presentan, se seleccionan independientemente del grupo que consiste en flúor, cloro, -OH, $-NH_2$, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino.

3. El compuesto de conformidad con la reivindicación 1 o 2, que tiene la Fórmula II:



II

en donde:

R^{37} se selecciona del grupo que consiste en alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilo, mono-alquilamino, di-alquilamino, cicloalquilamino, heterocicloalquilamino, fenilo opcionalmente sustituido con uno o más R^{41} y heteroarilo opcionalmente sustituido con uno o más R^{42};

R^{38} es hidrógeno, flúor, cloro o alquilo inferior opcionalmente sustituido con uno o más flúor;

R^{39} y R^{40} se seleccionan cada uno independientemente del grupo que consiste en flúor, cloro, -CN, -OH, $-NH_2$, alcoxi inferior, alquilo inferior opcionalmente sustituido con uno o más R^{43}, alquenilo inferior opcionalmente sustituido con C(O)-O-R^{44}, alquinilo inferior opcionalmente sustituido con alquilo inferior opcionalmente sustituido con uno o más flúor, o, en un carbono no de alquinilo del mismo, R^{45}, alcoxi inferior opcionalmente sustituido con R^{46}, mono-alquilamino, di-alquilamino, cicloalquilamino, cicloalquilalquilo-NH-, heterocicloalquilamino y heterocicloalquilalquilo-NH-;

cada R^{41}, cuando se presenta, se selecciona independientemente del grupo que consiste en halógeno, -CN, $-NO_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, -C(O)-O-R^{47}, -N(H)-C(O)-R^{48}, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior; o dos R^{41} en carbonos adyacentes se combinan para formar un heterocicloalquilo fusionado opcionalmente sustituido con uno o más alquilo inferior;

cada R^{42}, cuando se presenta, se selecciona independientemente del grupo que consiste en alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, -C(O)-O-R^{49}, y heteroarilo opcionalmente sustituido con uno o más alquilo inferior;

cada R^{43}, cuando se presenta, se selecciona independientemente del grupo que consiste en flúor, -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino;

cada R^{44}, cuando se presenta, es independientemente hidrógeno o alquilo inferior opcionalmente sustituido con uno o más flúor;

cada R^{45}, cuando se presenta, se selecciona independientemente del grupo que consiste en -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino;

cada R^{46}, cuando se presenta, se selecciona independientemente del grupo que consiste en -OH, alcoxi inferior, mono-alquilamino, di-alquilamino, cicloalquilamino, y heterocicloalquilamino;

cada R^{47}, cuando se presenta, es independientemente hidrógeno o alquilo inferior opcionalmente sustituido con uno o más flúor;

cada R^{48}, cuando se presenta, es independientemente alquilo inferior opcionalmente sustituido con uno o más flúor; y

cada R^{49}, cuando se presenta, es independientemente hidrógeno o alquilo inferior opcionalmente sustituido con uno o más flúor.

4. El compuesto de conformidad con la reivindicación 3, en donde R^{37} es alquilo inferior, alquilo inferior sustituido con flúor o fenilo, opcionalmente sustituido con de 1-3 grupos R^{41}.

5. El compuesto de conformidad con la reivindicación 4, en donde R^{37} es alquilo inferior, alquilo inferior sustituido con flúor o fenilo sustituido con de 1-3 grupos seleccionados de flúor, cloro, -CN, -NO_2, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, -C(O)-O-R^{47} o -N(H)-C(O)-R^{48}.

6. El compuesto de conformidad con la reivindicación 5, en donde R^{37} es alquilo inferior o fenilo sustituido con de 1-2 grupos seleccionados de flúor, cloro, -CN, -NO_2, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior o alcoxi inferior sustituido con flúor.

7. El compuesto de conformidad con la reivindicación 3, en donde R^{38} es H, -F o alquilo inferior sustituido con flúor.

8. El compuesto de conformidad con la reivindicación 3, en donde R^{39} es flúor, cloro, -CN, -OH, -NH_2, alcoxi inferior, alquilo inferior opcionalmente sustituido con uno o más R^{43}, cicloalquilamino, cicloalquilalquilo-NH-, heterocicloalquilamino y heterocicloalquilalquilo-NH-.

9. El compuesto de conformidad con la reivindicación 3, en donde R^{40} es H, alquilo inferior opcionalmente sustituido con uno o más R^{43}, halógeno, alcoxi inferior o –CN.

10. El compuesto de conformidad con cualquiera de las reivindicaciones 3-9, en donde R^{37} es alquilo inferior o fenilo opcionalmente sustituido con 1-2 miembros seleccionados de CF_3 o halógeno.

11. El compuesto de conformidad con la reivindicación 10, en donde R^{37} es propilo, 2-trifluorometilfenilo, 3-trifluorometilfenilo, 4-trifluorometilfenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo o fenilo 2,5-difluoro-sustituido.

12. El compuesto de conformidad con la reivindicación 11, en donde R^{37} es propilo, 4-trifluorometilfenilo, 2-fluorofenilo, 3-fluorofenilo o fenilo 2,5-difluoro-sustituido.

13. El compuesto de conformidad con cualquiera de las reivindicaciones 3-9, en donde R^{38} es H, F o CF_3.

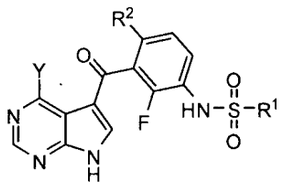
14. El compuesto de conformidad con cualquiera de las reivindicaciones 3-9, en donde R^{38} es F.

15. El compuesto de conformidad con cualquiera de las reivindicaciones 3-9, en donde R^{39} es flúor, cloro, -CN, -OH, -NH_2, alquilo inferior opcionalmente sustituido con flúor, alcoxi inferior, cicloalquilamino, cicloalquilalquilo-NH-, heterocicloalquilamino y heterocicloalquilalquilo-NH-.

16. El compuesto de conformidad con la reivindicación 15, en donde R^{39} es flúor, cloro, -CN, -OH, -NH_2, CH_3, CH_3O-, CF_3, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclopropilmetilo, ciclobutilmetilo, ciclopentilmetilo, ciclohexilmetilo, ciclopropilamino, ciclobutilamino, ciclopentilamino,

ciclohexilamino, ciclopropilmetilamino, ciclobutilmetilamino, ciclopentilmetilamino, ciclohexilmetilamino, 2-tetrahidrofuranilamino, 3-tetrahidrofuranilamino o 4-tetrahidropiranilamino.

17. El compuesto de conformidad con la reivindicación 1 o 2, que tiene la Fórmula III:



III

18. El compuesto de conformidad con cualquiera de las reivindicaciones 1, 2 o 17, en donde X se selecciona del grupo que consiste en –N=, –CH=, -C(CH_3)=, -C(OCH_3)=, -C(F)=, -C(CN)=, -C(CH_2OH)= y –C(Cl)=.

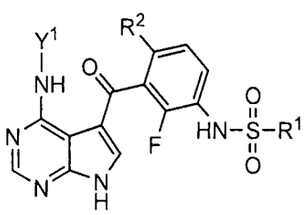
19. El compuesto de conformidad con cualquiera de las reivindicaciones 1, 2 o 17, en donde X es –N=, –CH=, -C(CH_3)=, -C(F)= o -C(CN)=.

20. El compuesto de conformidad con cualquiera de las reivindicaciones 1, 2 o 17, en donde X es –N=.

21. El compuesto de conformidad con cualquiera de las reivindicaciones 1, 2 o 17, en donde Y es flúor, cloro, bromo, yodo, alquilo inferior, alcoxi inferior, haloalquilo, CN, -OH, cicloalquilo, -OR^8 o –NH(R^4).

22. El compuesto de conformidad con cualquiera de las reivindicaciones 1, 2 o 17, en donde Y es CH_3, etilo, metoxi, etioxi, isobutilo, CN, OH, F, Cl, Br, I, NH_2, butioxi, 2-metilpropoxi, 4-tetrahidropiraniloxi, 2-tetrahirofuraniloxi, 3-tetrahirofuraniloxi, alcoxiamino o HO-NH-.

23. El compuesto de conformidad con las reivindicaciones 1 o 2, que tiene la Fórmula IIIa:



IIIa

en donde Y^1 es alquilo inferior opcionalmente sustituido con de uno a tres R^{11}, cicloalquilo, cicloalquilalquilo, arilo, arilalquilo, heterocicloalquilo, heterocicloalquilalquilo, heteroarilo o heteroarilalquilo, en donde:

(v) el cicloalquilo y cicloalquilalquilo se sustituyen cada uno opcionalmente con de uno a tres R^{12};

(vi) el heterocicloalquilo y heterocicloalquilalquilo se sustituyen cada uno opcionalmente con de uno a tres R^{13};

(vii) el arilo y arilalquilo se sustituyen cada uno opcionalmente con de uno a tres R^{14} opcionalmente, en donde los dos grupos R^{14} adyacentes en el anillo arilo se toman en conjunto para formar un anillo hetero aromático de 5 o 6 miembros que tiene de 1-4 heteroátomos seleccionados de O o N; y

(viii) el heteroarilo y heteroarilalquilo se sustituyen cada uno opcionalmente con de uno a tres R^{15};

24. El compuesto de conformidad con la reivindicación 23, en donde Y^1 se selecciona de alquilo inferior, alquilo inferior sustituido con halógeno, 2-hidroxietilo, ciclopropilamino, ciclobutilo, ciclopropilmetilo, ciclobutilmetilo, ciclopentilo, ciclopentilmetilo, ciclohexilmetilo, ciclohexilo, 2-oxetanilo, 2-oxetanilmetilo, 3-oxetanilo, 3-oxetanilmetilo, 2-tetrahidrofuranilo, 3-tetrahidrofuranilo, 2-tetrahidropiranilo, 3-tetrahidropiranilo, 4-tetrahidropiranilo, 2-tetrahidrofuranilmetilo, 3-tetrahidrofuranilmetilo, 2-tetrahidropiranilmetilo, 3-tetrahidropiranilmetilo, 4-tetrahidropiranilmetilo, 1-metil-2-aziridinilo, 1-metil-2-aziridinilmetilo, 1-metil-2-azetidinilo, 1-metil-2-azetidinilmetilo, 1-metil-3-azetidinilo, 1-metil-3-azetidinilmetilo, 1-metil-2-pirrolidinilo, 1-metil-2-pirrolidinilmetilo, 1-metil-3-pirrolidinilo, 1-metil-3-pirrolidinilmetilo, 1-metil-2-piperidinilo, 1-metil-2-piperidinilmetilo, 1-metil-3-piperidinilo, 1-metil-3-piperidinilmetilo, 1-metil-4-piperidinilo, 1-metil-4-piperidinilmetilo, 1-metilsulfonil-2-piperidinilo, 1-metilsulfonil-2-piperidinilmetilo, 1-metilsulfonil-3-piperidinilo, 1-metilsulfonil-3-piperidinilmetilo, 1-metilsulfonil-4-piperidinilo, 1-metilsulfonil-4-piperidinilmetilo, 1,1-dioxo-4-tianilo, 1,1-dioxo-4-tianilmetilo, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-bencilo, 2-fluorobencilo, 3-fluorobencilo, 4-fluorobencilo, 2-piridilo, 2-piridilmetilo, 3-piridilo, 3-piridilmetilo, 4-piridilo, 4-piridilmetilo, 2-clorofenilo, 3-clorofenilo, 4-clorofenilo, 2-dimetilaminofenilo, 3-dimetilaminofenilo, 4-dimetilaminofenilo, 2-dimetilaminobencilo, 2-dimetilaminobencilo, 3-dimetilaminobencilo, 4-dimetilaminobencilo, 2-hidoxifenilo, 3-hidoxifenilo, 4-hidoxifenilo, 2-hidroxibencilo, 3-hidroxibencilo, 4-hidroxibencilo, 2-carboxifenilo, 3-carboxifenilo, 4-carboxifenilo, 2-carboxibencilo, 3-carboxibencilo, 4-carboxibencilo, 2-metoxicarbonilfenilo, 3-metoxicarbonilfenilo, 4-metoxicarbonilfenilo, 2-metoxicarbonilbencilo, 3-metoxicarbonilbencilo, 4-metoxicarbonilbencilo, 1-alquil-4-pirazolilo, 1-alquil-4-pirazolilmetilo, 3-piridazinilo, piridazinilmetilo, 4-piridazinilo, 4-piridazinilmetilo, triazolilo, triazolimetilo, tetrazolilo, tetrazolimetilo, 2,1,3,-benzoxadiazolilo, 2,1,3-benzoxadiazol-5-ilo, 2,1,3,-benzoxadiazolil-metilo, 2,1,3-benzoxadiazol-5ilmetilo, 2,1,3,-benzotiadiazolilo, 2,1,3-benzotiadiazol-5-ilo, 2,1,3,-benzotiadiazolil-metilo, 2,1,3-benzotiadiazol-5ilmetilo, 1H-1,2,4-triazol-5-ilo, 1H-1,2,4-triazol-5-metilo, 2-oxobencimidazol-4-ilo, 2-oxobencimidazol-4-metilo, 2-oxobencimidazol-5-ilo, 2-oxobencimidazol-5-metilo, 1,1,-dioxo-tiolan-3-ilo, 1,1-dioxotiolan-3-metilo, 3-(2-metil-1,2,3,4-tetrazol-5-il)fenilo, 3-(2-metil-1,2,3,4-tetrazol-5-il)bencilo, 3-(5-metil-1,2,3,4-tetrazol-1-il)fenilo, 3-(1,2,4-triazol-5-il)fenilo, 3-(1,2,,4-triazol-5-il)bencilo, 3-3-metil-4H-1,2,4-triazol-5-metilo o 2-(3-metil-4H-1,2,4-triazol-5-il)etilo.

25. El compuesto de conformidad con cualquiera de las reivindicaciones 17-23 o 24, en donde R^2 es H o F.

26. El compuesto de conformidad con cualquiera de las reivindicaciones 17-23 o 24, en donde R^1 es alquilo inferior, cicloalquilo opcionalmente sustituido con 1-2 grupos seleccionados de halógeno o

alquilo inferior, heterocicloalquilo, heteroarilo opcionalmente sustituido con alquilo inferior o alcoxi inferior, fenilo opcionalmente sustituido con 1-2 sustituyentes seleccionados de alquilo inferior, halógeno, alcoxi inferior, haloalquilo, haloalcoxi o CN.

27. El compuesto de conformidad con la reivindicación 26, en donde R^1 es metilo, propilo, isobutilo, 2-metilpropilo, CF_3, CF_3CH_2-, CHF_2CH_2-, 4-trifluorofenilo, 2-trifluorofenilo, 3-trifluorofenilo, 3,5-dimetilfenilo, 4-propilfenilo, 3-fluoro-4-metoxifenilo, 2-cianofenilo, 3-cianofenilo, 4-cianofenilo, 4-fluoro-3-metoxifenilo, 2,5-difluorofenilo, 2,6-difluorofenilo, 2,4-difluorofenilo, 2-piridilo, 3-piridilo, 5-metoxi-2-piridilo, 3-metoxi-2-piridilo, 4-metoxi-2-piridilo, 6-metil-2-piridilo, 5-metil-2-piridilo, 4-metil-2-piridilo, 3-metil-2-piridilo, dialquilamino, 1-pirrolidinilo, 1-piperidinilo, 4-morfolinilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, 4,4-difluorociclohexilo, 1-metil-4-pirazolilo, 1-etil-4-pirazolilo, 1-metil-3-pirazolilo, 1-etil-3-pirazolilo, 6-metil-3-piridilo, 5-metil-3-piridilo, 4-metil-3-piridilo o 2-metil-3-piridilo.

28. El compuesto de conformidad con la reivindicación 27, en donde R^1 es 2-fluorofenilo, 3-fluorofenilo, 2,5-difluorofenilo o fenilo 4-alquilo inferior-sustituido, en donde el alquilo inferior se sustituye opcionalmente con uno o más flúor.

29. El compuesto de conformidad con cualquiera de las reivindicaciones 17-22, en donde Y es $-NR^3R^4$, en donde R^3 y R^4 se combinan con el átomo de nitrógeno al cual se unen para formar un anillo de tres a siete miembros que tiene 0-1 heteroátomo adicional seleccionado de O, N o S, en donde los átomos de nitrógeno y azufre se oxidan opcionalmente.

30. El compuesto de conformidad con la reivindicación 29, en donde Y es 1-aziridinilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidinilo, 1-morfolinilo o 1-azepanilo.

31. Un compuesto seleccionado del grupo que consiste en:
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (P-1001),
Ácido propano-1-sulfónico [3-(4-etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (P-1002),
ácido 2-Metil-propano-1-sulfónico [2,4-difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (P-1003),
ácido 2-Metil-propano-1-sulfónico [2,4-difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (P-1004),
N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida (P-1005),
N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (P-1006),
N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida (P-1007),
N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida (P-1008),

N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida (P-1009),

N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-isopropil-bencenosulfonamida (P-1010),

N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (P-1012),

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-isobutil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (P-1014),

N-[2,4-Difluoro-3-(4-isobutil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (P-1015),

N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (P-1016),

ácido 6-Metoxi-piridin-3-sulfónico [2,4-difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (P-1018),

N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-etil-bencenosulfonamida (P-1019),

N-{2,4-Difluoro-3-[4-(tetrahidro-piran-4-iloxi)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-fenil}-4-trifluorometil-bencenosulfonamida (P-1021),

Ácido propano-1-sulfónico [2,4-difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-amida (P-1022),

N-[3-(4-Ciano-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-bencenosulfonamida (P-1023),

N-[2,4-Difluoro-3-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3,5-dimetil-bencenosulfonamida (P-1025),

N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3,5-dimetil-bencenosulfonamida (P-1027),

N-[2,4-Difluoro-3-(4-isobutoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (P-1028),

N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (P-1029),

N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-4-propil-bencenosulfonamida (P-1030),

Ácido propano-1-sulfónico [3-(4-cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-amida (P-1033),

N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (P-1034),

N-[2,4-Difluoro-3-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-3-fluoro-4-metoxi-bencenosulfonamida (P-1036),

N-[3-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-propil-bencenosulfonamida (P-1038),

N-[3-(4-Ciclopropilmetoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-4-trifluorometil-

bencenosulfonamida (P-1053),
N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2-fluoro-bencenosulfonamida (P-1070),
N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2-fluoro-bencenosulfonamida (P-1071),
N-[3-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (P-1107),
N-[3-(4-Ciclopropilmetoxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (P-1181),
N-[2,4-Difluoro-3-(4-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (P-1182),
N-[2,4-Difluoro-3-(4-hidroxi-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-fenil]-2,5-difluoro-bencenosulfonamida (P-1183),
N-[3-(4-Cloro-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-2,4-difluoro-fenil]-2,5-difluoro-bencenosulfonamida (P-1184),
Ácido propano-1-sulfónico [2,4-difluoro-3-(4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-amida (P-2015),
N-[2,4-Difluoro-3-(4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-4-trifluorometil-bencenosulfonamida (P-2016),
N-[2,4-Difluoro-3-(4-trifluorometil-1H-pirrolo[2,3-b]piridin-3-carbonil)-fenil]-bencenosulfonamida (P-2017), y

cualquier sal farmacéuticamente aceptable de los mismos.

32. Una composición que comprende un compuesto de cualquiera de las reivindicaciones 1-31 y un excipiente o portador farmacéuticamente aceptable.

33. Una composición farmacéutica que comprende un compuesto de cualquiera de las reivindicaciones 1-31 y otro fármaco.

34. Un kit que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1-31 o una composición de acuerdo con la reivindicación 32 o 33.

35. Un método para tratar una enfermedad o padecimiento mediado por proteína cinasa Raf en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-31 o una composición de las reivindicaciones 32 o 33.

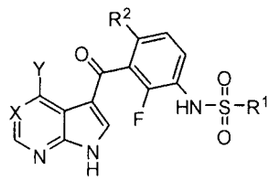
36. Un método para tratar una enfermedad o padecimiento mediado por proteína cinasa Raf en un sujeto en necesidad de ello, el método comprende administrar al sujeto una cantidad efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-31 y otro fármaco o una sal farmacéuticamente aceptable del mismo.

37. El método de conformidad con la reivindicación 35 o 36, en donde la enfermedad o padecimiento se selecciona del grupo que consiste en demencia vascular, lesión en cabeza, lesión en médula espinal, enfermedad de Alzheimer (AD), enfermedad de Parkinson, ataques y epilepsia; enfermedades neoplásicas incluyendo, pero sin limitarse a, melanoma, glioma, sarcoma, carcinoma (por ejemplo, gastrointestinal, de hígado, conducto biliar (colangiocarcinoma), colorectal, pulmón, mama, pancreático, tiroideo, renal, ovárico, próstata), linfoma (por ejemplo, linfoma histiocítico) neurofibromatosis, leucemia mieloide aguda, síndrome mielodisplásico, leucemia, angiogénesis tumoral, tumores neuroendocrinos tales como cáncer de tiroides medular, carcinoide, cáncer de pulmón de células pequeñas, sarcoma de Kaposi, y feocromocitoma; dolor de origen neuropático o inflamatorio, incluyendo, pero sin limitarse a, dolor agudo, dolor crónico, dolor relacionado con cáncer, y migraña; enfermedades cardiovasculares incluyendo, pero sin limitarse a, falla cardiaca, apoplejía isquémica, hipertrofia cardiaca, trombosis (por ejemplo, síndromes de microangiopatía trombótica), ateroesclerosis, y lesión por reperfusión; inflamación y/o proliferación incluyendo, pero sin limitarse a, psoriasis, eczema, artritis y enfermedades y padecimientos autoinmunes, osteoartritis, endometriosis, cicatrización, restenosis vascular, trastornos fibróticos, artritis reumatoide, enfermedad intestinal inflamatoria (IBD); enfermedades por inmunodeficiencias, incluyendo, pero sin limitarse a, rechazo de transplantes de órganos, enfermedad injerto versus huésped, y sarcoma de Kaposi asociado con HIV; enfermedades renales, quísticas, o prostáticas, incluyendo, pero sin limitarse a, nefropatía diabética, enfermedad renal poliquística, nefroesclerosis, glomerulonefritis, hiperplasia de próstata, enfermedad de hígado poliquístico, esclerosis tuberosa, enfermedad de Von Hippel Lindau, enfermedad renal medular quística, nefronoftisis, y fibrosis quística; trastornos metabólicos, incluyendo, pero sin limitarse a, obesidad; infección, incluyendo, pero sin limitarse a, *Helicobacter pylori*, virus de Hepatitis e Influenza, fiebre, HIV, y septicemia; enfermedades pulmonares incluyendo, pero sin limitarse a, enfermedad pulmonar obstructiva crónica (COPD) y síndrome de insuficiencia respiratoria aguda (ARDS); enfermedades genéticas del desarrollo, incluyendo, pero sin limitarse a, síndrome de Noonan, síndrome de Costello, (síndrome faciocutaneoesquelético), síndrome LEOPARD, síndrome cardio-faciocutáneo (CFC), y anormalidades del síndrome de crestas neurales que provocan enfermedades cardiovasculares, esqueléticas, intestinales, de piel, cabello y endocrinas; y enfermedades asociadas con regeneración o degeneración muscular, incluyendo, pero sin limitarse a, sarcopenia, distrofias musculares (incluyendo, pero sin limitarse a, Distrofias de Duchenne, Becker, Emery-Dreifuss, de Cintura Pélvica, Facioescapulohumeral, Miotónica, Oculofaríngea, Distal y Muscular Congénita), enfermedades de neuronas motoras (incluyendo, pero sin limitarse a, esclerosis lateral amiotrófica, atrofia muscular espinal progresiva infantil, atrofia muscular espinal intermedia, atrofia muscular espinal juvenil, atrofia muscular bulbar espinal, y atrofia muscular espinal adulta), miopatías inflamatorias (incluyendo, pero sin limitarse a, dermatomiositis, polimiositis, y miositis por cuerpos de inclusión), enfermedades de la placa neuromuscular (incluyendo, pero sin limitarse a, miastenia grave, síndrome de Lambert-Eaton, y síndrome miasténico congénito), miopatías debido a anormalidades endocrinas (incluyendo, pero sin limitarse a, miopatía hipertiroidea y miopatía hipotiroidea) enfermedades de nervios periféricos (incluyendo, pero sin limitarse a, enfermedad de Charcot Marie Tooth, enfermedad de Dejerine-Sottas, y ataxia de Friedreich), otras miopatías (incluyendo, pero sin limitarse a, miotonía congénita, paramiotonía congénita, enfermedad de núcleo central, miopatía nemalínica, miopatía miotubular, y parálisis

periódica), y enfermedades metabólicas de músculo (incluyendo, pero sin limitarse a, deficiencia de fosforilasa, deficiencia de maltasa ácida, deficiencia de fosfofructocinasa, deficiencia de enzima de desconexión, miopatía mitocondrial, deficiencia de carnitina, deficiencia de carnitina palmatilo transferasa, deficiencia de fosfoglicerato cinasa, deficiencia de fosfoglicerato mutasa, deficiencia de lactato deshidrogenasa, y deficiencia de mioadenilato desaminasa).

38. El método de conformidad con la reivindicación 37, en donde la enfermedad o padecimiento se selecciona del grupo que consiste en melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, cáncer colorrectal, cáncer de tiroides, cáncer de pulmón, cáncer ovárico, cáncer de próstata, cáncer de hígado, cáncer de vesícula biliar, tumores de estroma gastrointestinal, cáncer del tracto biliar, cáncer testicular y colangiocarcinoma.

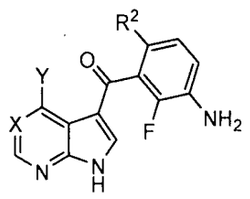
39. Un método para preparar un compuesto de la Fórmula I de acuerdo con la reivindicación 1



I

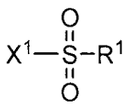
el método comprende:

poner en contacto un compuesto de la Fórmula IVc:



IVc

con un compuesto de la Fórmula V:



V

bajo condiciones suficientes para formar el compuesto de la Fórmula I, en donde:

X^1 es un halógeno.

40. El método de conformidad con la reivindicación 39, en donde X es –N=, –CH=, -$C(CH_3)$=, -$C(OCH_3)$=, -C(F)=, -C(CN)=, -$C(CH_2OH)$= o –C(Cl)=.

RESUMEN

Se describen compuestos y sales de los mismos, formulaciones de los mismos, conjugados de los mismos, derivados de los mismos, formas de los mismos y usos de los mismos. En ciertos aspectos y modalidades, los compuestos descritos o sales de los mismos, formulaciones de los mismos, conjugados de los mismos, derivados de los mismos, formas de los mismos son activos sobre por lo menos una proteína cinasa Raf. En ciertos aspectos y modalidades, los compuestos descritos son activos en la inhibición de la proliferación de una línea celular mutante de Ras. También se describen métodos de uso de los mismos para tratar enfermedades y padecimientos, incluyendo enfermedades y padecimientos asociados con la actividad de la proteína cinasa mutante B-Raf V600E, incluyendo melanoma, glioma, glioblastoma multiforme, astrocitoma pilocítico, cáncer colorrectal, cáncer de tiroides, cáncer de pulmón, cáncer ovárico, cáncer de próstata, cáncer de hígado, cáncer de vesícula biliar, tumores de estroma gastrointestinal, cáncer del tracto biliar, y colangiocarcinoma. También se describen métodos de uso de los mismos para tratar enfermedades y padecimientos, incluyendo enfermedades y padecimientos asociados con la actividad de la proteína cinasa c-Raf-1, incluyendo dolor agudo, dolor crónico o enfermedad renal poliquística.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

REITER, Stephen, E.
Foley & Lardner LLP
3579 Valley Centre Drive, Suite 300
San Diego, California 92130
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*	
11 March 2011 (11.03.2011)	
Applicant's or agent's file reference 039363-5504	**IMPORTANT NOTIFICATION**
International application No. PCT/US2010/057293	International filing date *(day/month/year)* 18 November 2010 (18.11.2010)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
ZHANG, Chao 397 Springfield Plaza Moraga, CA 94556 United States of America	CN	US
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☒ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
ZHANG, Chao 397 Springfield Plaza Moraga, CA 94556 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Sontag Frederic
Facsimile No. +41 22 338 70 90	e-mail pt12.pct@wipo.int Telephone No. +41 22 338 74 12

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 039363-5504	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 10/57293	International filing date *(day/month/year)* 18 November 2010 (18.11.2010)	(Earliest) Priority Date *(day/month/year)* 18 November 2009 (18.11.2009)
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. _____

   ☐ 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/US 10/57293

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.: 10-16, 18-22, 25-30 and 32-38
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/US 10/57293

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/90; A61K 31/519 (2010.01)
USPC - 514/265.1
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)
USPC: 514/265.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/256, 258.1, 427 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Database Searched: PUBWEST (PGPUB, EPAB, JPAB, USPT). Search Terms Used pyrimidine$ near4 $pyrrolo, $benzene sulfonamide, trifluoromethylbenzene sulfonamide, benzenesulfonamide, head injury, spinal cord injury, acute pain, chronic pain, cancer-related pain, migraine, atherosclerosis, reperfusion injury, psoriasis, eczema, arthritis, aut

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2008/0167338 A1 (Spevak et al.) 10 July 2008 (10.07.2008) entire document especially para [0009]-[0012]	1-9, 17, 23-24, 31, 39-40
Y	US 5,958,930 A (Gangjee) 28 September 1999 (28.9.1999) especially figure 1 and 2	1-9, 17, 23-24, 31, 39-40
Y	US 2009/0076046 A1 (Zhang et al.) 19 March 2009 (19.03.2009) especially para [1140], scheme 21	39-40
P/X	US 2009/0286783 A1 (Ibrahim et al.) 19 November 2009 (19.11.2009) entire document	1-9, 17, 23-24, 31

☐ 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
09 January 2011 (09.01.2011)	25 JAN 2011
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: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-081901- -00000-0000

Fecha: 2012-05-17 16:43:40 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 271

Act. 411 PRESENTACION Folios: 270

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ Art 33 Decisión 486/00

- ☐ 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 ☐