Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE

INVENC

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-187143- -00000-0000

Fecha: 2012-10-22 16:26:02 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 35

TITULO: COMPUESTOS Y MÉTODOS PARA LA MODULACIÓN DE QUINASA E INDICACIONES DE LA MISMA.

SOLICITANTE: PLEXXIKON, INC.

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

APODERADO: CARLOS R. OLARTE

BOGOTÁ 22 de October de 2012

P2012/000126

OLARTEMOURE

OLARTE MOURE & ASOCI.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-187143- -00000-0000

Fecha: 2012-10-22 16:26:02 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 3

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2012/000126**

SOLICITUD DE:

(1)

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

[X] Capítulo I. [ ] Capítulo II.

(2)

SOLICITANTE (71)

Nombre: PLEXXIKON, INC.

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

Nacionalidad o Domicilio Estados Unidos de América

Lugar de Constitución: Estados Unidos de América

Teléfono: _____ **Fax:** _____

E-mail: _____

IDENTIFICACIÓN

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

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

Cual _____

Número _____

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE

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

Teléfono: 601-7700 **Fax:** 601-7799

E-mail: office@olartemoure.com

IDENTIFICACIÓN

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

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

Cual _____

Número 79782747Bta

TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2011/033192 Fecha Abril 20, 2011

Publicación Internacional No. WO 2011/133637 A3 Fecha Octubre 27, 2011

(6) **Título (54)** **COMPUESTOS Y MÉTODOS PARA LA MODULACIÓN DE QUINASA E INDICACIONES DE LA MISMA.**

Clasificación Internacional (51) C07D 471/04; C07D 487/04; A61K 31/437; A61K 31/506, A61K 31/519; A61P 19/00; A61P 25/00; A61P 35/00.

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Abril 21, 2010	61/326.626

(9) **Comprobante de pago No.** 12- **Fecha** _____

(10) **ANEXOS**

X	Comprobante de pago de la tasa de presentación de la solicitud.
	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
	Poderes, si fuere el caso. Adjunto copia simple Ver Expediente No.
	Documento de cesión del inventor al solicitante o a su causante.
X	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.
	De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
	De ser el caso, certificado de depósito del material biológico.
	Arte final 12 x 12.
	De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
X	De ser el caso, modificaciones efectuadas a la solicitud internacional. Formulario PCT/IB/306
X	Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/US2011/033192

Jiazhong ZHANG
888 Foster City Blvd., Apt. Q4,
Foster City, CA 94404
Estados Unidos de América
Nacionalidad: Republica Popular de China

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

James TSAI
25 Southport Way
Vallejo, CA 94591
Estados Unidos de América
Nacionalidad: Estadounidense

Todd EWING
20 Edmund Ct.
Walnut Creek, CA 94596
Estados Unidos de América
Nacionalidad: Estadounidense

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

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

35

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 107703

Bogotá D.C., Octubre 12 de 2012 - 15:43:52

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	494783656	12/10/2012	8.447.500.00

*** 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. 12-187143- -00000-0000

Fecha: 2012-10-22 16:26:02 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 35

Industria y Comercio
SUPERINTENDENCIA

RELACIÓN DE ANEXOS

Dependencia:	Fecha: _____/ _____/ _____/ AAAA MM DD	Recorrido:
Tipo de Radicación: Entrada: ☐ Salida: ☐ Traslado: ☐ Convenio: ☐		
Radicador:		Planilla:

ID	No. Radicación	Consecutivo	Item
1	12-187143	0	
2			
3			
4			
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14			
15			
16			
17			

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

Observaciones:

Anexo CD.

Nota del Traductor:

El poder otorgado por Plexxikon Inc. a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro, tiene los siguientes textos, firmas y sellos en inglés:

Manuscrito: "Ver reconocimiento adjunto"

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

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

www.sdarcc.com

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

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

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

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

Fecha: 1º de Junio de 2006.

Firmado en constancia,

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

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

Oficinas disponibles para servirle:

Chula Vista	El Cajon	Kearny Mesa	San Marcos

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

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

Sello.

Apostilla adjunta:

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

ESTADO DE CALIFORNIA
Secretario de Estado

APOSTILLA

(Convention du La Haye du 5 octobre 1961)

1. País: ESTADOS UNIDOS DE AMÉRICA

El presente documento público

2. Ha sido firmado por: Gregory J. Smith

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

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

Certificado

5. En: San Diego, California

6. El: Día primero de Junio de 2006

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

8. Bajo el No. 137876

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

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

Sello pequeño: "Oficina del Secretario de Estado"

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

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

State of California

SECRETARY OF STATE
APOSTILLE

(Convention de La Haye du 5 octobre 1961)

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

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

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

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

CERTIFIED

5. *At SAN DIEGO, California*

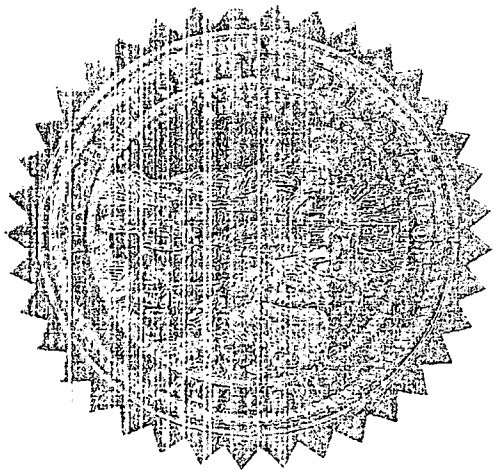
6. *The 1ST day of JUNE, 2006*

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

8. *No. 137876*

9. *Stamp/Seal*

10. *Signature*





Bruce McPherson

Secretary of State

BY Carolyn J. Johnson

Gregory J. Smith

COUNTY OF SAN DIEGO

ASSESSOR / RECORDER / COUNTY CLERK

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

www.sdarcc.com

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

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

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

DATED: June 1, 2006 Witness by hand

GREGORY J SMITH, County Assessor/Recorder/Clerk

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

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

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

Of Counsel
Guillermo Chahín
Graciela Melo

Power of Attorney

Poder

The undersigned, domiciled in

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

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

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

Signature/Firma:

Date/Fecha: 1/16/06

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

See attached acknowledgment

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

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

1. That

Dean R. Artis

of legal age and domiciled in

91 Bolivar Drive, Berkeley, California 94710 USA

signed the foregoing document.

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

3. That Plexxikon, Inc., having its principal place of business located in Berkeley, CA United States is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

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

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

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

Dean R. Artis

mayor de edad y domiciliado

91 Bolivar Drive, Berkeley, California 94710 USA

suscribió el documento que antecede.

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

4. Que
con sede principal ubicada en

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

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

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

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

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

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

Nota del Traductor:

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

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

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

www.sdarcc.com

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

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

Traductor Oficial
JORGE ENRIQUE SIERRA REYES

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

Fecha: 8 de Mayo de 2006.

Firmado en constancia,

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

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

Oficinas disponibles para servirle:

Chula Vista	El Cajon	Kearny Mesa	San Marcos

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

La suscrita, Kathleen Sereda Glaub, certifica lo siguiente:

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

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1002

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

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

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

RECONOCIMIENTO PARA TODOS LOS PROPÓSITOS DE CALIFORNIA

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

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

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

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

Apostilla adjunta:

ESTADO DE CALIFORNIA
Secretario de Estado

APOSTILLA

(Convention du La Haye du 5 octobre 1961)

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

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

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

State of California

SECRETARY OF STATE
APOSTILLE

(Convention de La Haye du 5 octobre 1961)

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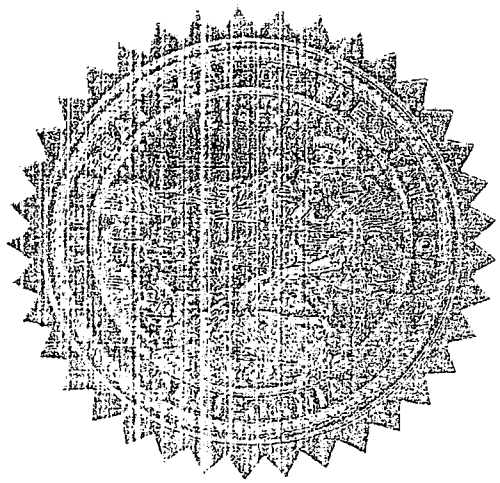
6. *The 8TH day of MAY, 2006*

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

8. *No. 137384*

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Bruce McPherson

Secretary of State

BY Cheryl Miller



HI-24 A (REV 4-05)

OSP 05 90772

Gregory J. Smith

COUNTY OF SAN DIEGO

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

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

DATED: May 8, 2006 Witness by hand

GREGORY J SMITH, County Assessor/Recorder/Clerk

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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:

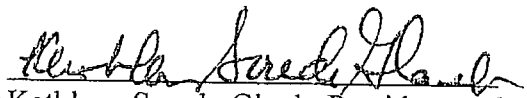
1. She is the duly elected, qualified and acting President and Secretary of Plexxikon Inc. a California corporation (the "***Company***"), and is familiar with the facts herein certified and is duly authorized to certify the same, and to make the statements as certified by her herein.

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 SERENA GL[illegible] (Name(s) of Signer(s))

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

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

WITNESS my hand and official seal.

Signature of Notary Public

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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 October 2011 (27.10.2011)

PCT

(10) International Publication Number
WO 2011/133637 A2

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61K 31/519* (2006.01)
C07D 487/04 (2006.01) *A61P 19/00* (2006.01)
A61K 31/437 (2006.01) *A61P 25/00* (2006.01)
A61K 31/506 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/US2011/033192

(22) International Filing Date:
20 April 2011 (20.04.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/326,626 21 April 2010 (21.04.2010) US

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

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2011/133637 A2

(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 one or more of Fms, Kit, Flt3, TrkA, TrkB and TrkC kinase protein. Also described are methods of use thereof to treat diseases and conditions, including diseases and conditions associated with activity of one or more of Fms, Kit, Flt3, TrkA, TrkB and TrkC, including rheumatoid arthiritis, osteoarthritis, osteoporosis, periprosthetic osteolysis, systemic sclerosis, demyelinating disorders, multiple sclerosis, Charcot Marie Tooth syndrome, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, ulcerative colitis, Crohn's disease, immune thrombocytopenic purpura, atherosclerosis, systemic lupus erythematosis, myelopreparation for autologous transplantation, transplant rejection, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, renal hypertrophy, type I diabetes, acute pain, inflammatory pain, neuropathic pain, acute myeloid leukemia, melanoma, multiple myeloma, breast cancer, prostate cancer, pancreatic cancer, lung cancer, ovarian cancer, gliomas, glioblastoma, neurofibromatosis, osteolytic bone metastases, brain metasteses, gastrointestinal stromal tumors, and giant cell tumors.

COMPOUNDS AND METHODS FOR KINASE MODULATION, AND INDICATIONS THEREFOR

FIELD OF THE INVENTION

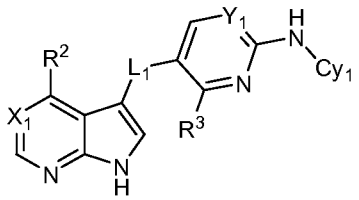
[0001] Disclosed are novel compounds and uses thereof. In certain embodiments disclosed compounds are kinase inhibitors.

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 certain embodiments, the compounds are active on one or more protein kinases, including Fms, Kit, Flt3, TrkA, TrkB and/or TrkC, including any mutations thereof. In certain embodiments, compounds are active on Fms kinase. In certain embodiments, compounds are active on Fms and Kit kinase. In certain embodiments, compounds are selectively active on Fms kinase relative to Kit kinase. In certain embodiments, compounds are active on Fms kinase and Flt3 kinase. In certain embodiments, compounds are active on Fms kinase and one or more of TrkA, TrkB and TrkC 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 of Fms, Kit, Flt3, TrkA, TrkB and TrkC, including any mutations thereof. Thus, the use of compounds for therapeutic methods involving modulation of protein kinases are provided. In certain embodiments, the compounds are used for therapeutic methods involving the treatment of a variety of indications, including, but not limited to, rheumatoid arthiritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, systemic sclerosis, demyelinating disorders, multiple sclerosis, Charcot Marie Tooth syndrome, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, ulcerative colitis, Crohn's disease, immune thrombocytopenic purpura, atherosclerosis, systemic lupus erythematosis, myelopreparation for autologous transplantation, transplant rejection, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, renal hypertrophy, type I diabetes, acute pain, inflammatory pain, neuropathic pain, acute myeloid leukemia, melanoma, multiple myeloma, breast cancer, prostate cancer, pancreatic cancer, lung cancer, ovarian cancer, gliomas, glioblastoma, neurofibromatosis, osteolytic bone metastases, brain metasteses, gastrointestinal stromal tumors, and giant cell tumors. In some embodiments, compounds are of Formula I as described below.

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



Formula I

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

X_1 is –N=, -C(H)=, or -C(R^1)= ;

Y_1 is –N= and R^3 is hydrogen; or Y_1 is-C(H)= and R^3 is fluoro or chloro;

L_1 is -C(H_2)- or -C(O)-;

Cy_1 is cycloalkyl optionally substituted with one or more R^4, phenyl optionally substituted with one or more R^5, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^6 and optionally substituted on an available nitrogen atom with R^7;

when X_1 is -C(R^1)=, R^2 is hydrogen;

when X_1 is –N= or -C(H)=, R^2 is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^8, -N(R^{9a})(R^{9b}), and -O-R^9;

R^1 is fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

each R^4 is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

each R^5 is independently selected from the group consisting of fluoro, chloro, -O-R^{10}, -S-R^{11}, -S(O_2)-R^{12}, and lower alkyl optionally substitituted with one or more R^{13};

each R^6 is independently selected from the group consisting of fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro; or two R^6 bound to adjacent carbon atoms of the heteroaryl ring, taken together, form a fused cycloalkyl ring;

R^7 is cycloalkyl, lower alkoxy or lower alkyl optionally substituted with one or more fluoro;

R^8 is fluoro or lower alkoxy optionally substitituted with one or more fluoro;

R^{9a} is H and R^{9b} is selected from the group consisting of (i) H, lower alkyl, lower alkyl substituted with one or more fluoro, lower alkyl substituted with lower alkoxy or lower alkyl substituted with hydroxyl and (ii) cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, each of which is optionally substituted with one to three members selected from lower alkyl, haloalkyl, lower alkoxy or fluoro; or

R^{9a} and R^{9b} together with the nitrogen to which they are attached form a 5- or 6-membered ring having from 0 to 1 additional heteroatom selected from O, N or S, each of which is optionally

substituted with one to three members selected from lower alkyl, haloalkyl, lower alkoxy or fluoro;

R^9 is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy;

each R^{10}, R^{11} and R^{12} are independently lower alkyl optionally substituted with one or more fluoro; and

each R^{13} is independently selected from the group consisting of fluoro, -OH, and lower alkoxy optionally substituted with one or more fluoro.

In some embodiments of compounds of Formula I, R^3 is fluoro. In certain embodiments, the salt is a pharmaceutically acceptable salt.

[0005] In some embodiments, the invention provides compounds of Formula I or any of the subformulas as described herein, or a pharmaceutically acceptable salt, a solvate, a tautomer or a stereoisomer thereof. In other embodiments of the invention, there are provided compounds of Formula I or any of the subformulas as described herein, or a pharmaceutically acceptable salt or a solvate thereof. In some embodiments, the solvate is a hydrate.

[0006] In some embodiments of compounds of Formula I, X_1 is –N= and R^2 is selected from the group consisting of cycloalkyl, lower alkyl optionally substituted with one or more R^8, for example, 1 to 3 R^8, and -O-R^9. In one embodiment, X_1 is –N= and R^2 is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, X_1 is –N= and R^2 is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, X_1 is -N= and R^2 is selected from the group consisting of methyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0007] In some embodiments of compounds of Formula I, X_1 is -C(H)= or -C(R^1)= and R^1 is fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro. In one embodiment, X_1 is -C(H)= or -C(R^1)= and R^1 is chloro or lower alkyl. In one embodiment, X_1 is -C(H)= or -C(R^1)= and R^1 is chloro or C_{1-3} alkyl. In one embodiment, X_1 is -C(H)= or -C(R^1)= and R^1 is chloro or methyl.

[0008] In some embodiments of compounds of Formula I, further to any of the above embodiments of Formula I, Cy_1 is cycloalkyl optionally substituted with one or more R^4, phenyl optionally substituted with one or more R^5, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^6 and optionally substituted on an available nitrogen atom with R^7, wherein cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and heteroaryl is pyridinyl or pyrazolyl.

[0009] In some embodiments of compounds of Formula I, further to any of the above embodiments of Formula I, Cy_1 is cycloalkyl optionally substituted with one or more R^4, phenyl optionally substituted with one or more R^5, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^6 and optionally substituted on an available nitrogen atom with R^7, wherein cycloalkyl is cyclohexyl, or cycloheptyl, and heteroaryl is pyridin-3-yl or pyrazol-4-yl.

[0010] In some embodiments of compounds of Formula I, further to any of the above embodiments of Formula I, L_1 is -C(H_2)-. In some embodiments of compounds of Formula I, further to any of the above embodiments of Formula I, L_1 is -C(O)-.

[0011] In some embodiments of compounds of Formula I, further to any of the above embodiments of Formula I, Y_1 is –N= and R^3 is hydrogen. In some embodiments of compounds of Formula I, further to any of the above embodiments of Formula I, Y_1 is-C(H)= and R^3 is fluoro.

[0012] In some embodiments (A) of compounds of Formula I, X_1 is N and all the other variables are as defined herein. Within embodiments (A), in certain instances, L_1 is CH_2, Y_1 is CH and R^3 is F. In other instances, L_1 is CH_2, Y_1 is N and R^3 is F. In yet other instances, L_1 is -C(=O)-, Y_1 is CH and R^3 is F. In still other instances, L_1 is -C(=O)-, Y_1 is N and R^3 is F.

[0013] In some embodiments (B) of compounds of Formula I, X_1 is –C(R^1)=, R^1 and all the other variables are as defined herein. Within embodiments (B), in certain instances, L_1 is CH_2, Y_1 is CH and R^3 is F. In other instances L_1 is -C(=O)-, Y_1 is CH and R^3 is F. In yet other instances, L_1 is –CH_2-, Y_1 is N and R^3 is F. In still other instances, L_1 is -C(=O)-, Y_1 is N and R^3 is F.

[0014] In some embodiments (C) of compounds of Formula I, X_1 is N, R^2 is -N(R^{9a})(R^{9b}), and all the other variables are as defined herein.

[0015] In some embodiments of compounds of Formula I, Cy_1 is cycloalkyl optionally substituted with one or more R^4. In certain instances, Cy_1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl, each of which is optionally substituted with from 1 to 3 R^4. All the other variables are as defined herein.

[0016] In some embodiments of compounds of Formula I, Cy_1 is phenyl optionally substituted with one or more R^5 and all the other variables are as defined herein.

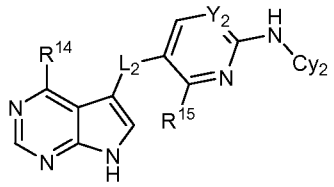
[0017] In some embodiments of compounds of Formula I, wherein Cy_1 is 5 or 6-membered heteroaryl optionally substituted on an available carbon atom with one or more R^6 and optionally substituted on an available nitrogen atom with R^7. In certain instances, Cy_1 is 3-pyridyl, 2-pyrrolyl, 3-pyrrolyl or 4-pyrazolyl, optionally substituted on an available carbon atom with from 1 to 3 R^6 and optionally substituted on an available nitrogen atom with R^7. In some embodiments, each R^6 is

independently selected from the group consisting of fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with from one to three fluoro, and lower alkoxy optionally substituted with one to three fluoro; or two R^6 bound to adjacent carbon atoms of the heteroaryl ring form a fused cycloalkyl ring. All the other variables are as defined herein.

[0018] In some embodiments of compounds of Formula I, R^{9a} is H and R^{9b} is selected from H, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with 1 to 3 fluoro groups, cycloalkyl optionally substituted with lower alkyl or one to three fluoro, cycloalkylalkyl optionally substituted with lower alkyl or one to three fluoro substituents, heterocycloalkyl optionally substituted with lower alkyl, heterocycloalkylalkyl, arylalkyl optionally substituted with from 1 to 3 members selected from lower alkyl, fluoro or haloalkyl and heteroarylalkyl optionally substituted with from one to three members selected from alkyl, fluoro or haloalkyl. In certain instances, R^{9a} is H and R^{9b} is selected from (i) H, methyl, ethyl, t-butyl, propyl, isopropyl, 2-butyl, n-butyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 3-methoxypropyl, 2,2,2-trifluoroethyl, or 4-methoxybutyl and (ii) cyclopropyl, cyclobutyl, cyclopentyl, cylohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexymethyl, benzyl, 1-methylbenzyl, 4,4-difluorocyclohexyl, 2-tetrahydrofuranylmethyl, 4-piperadinyl, 3-pyridyl, 2-pyridyl or 4-pyridyl,each of which is optionally substituted with from 1 to 3 members selected from lower alkyl, lower alkoxy, fluoro or CF_3. All the other variables are as defined herein.

[0019] In some embodiments of compounds of Formula I, $-N(R^{9a})(R^{9b})$ is 1-piperadinyl, 4-morpholinyl, 1-piperazinyl or 1-pyrrolidinyl, each of which is optionally substituted with one to three members selected from lower alkyl, haloalkyl, lower alkoxy or fluoro. All the other variables are as defined herein.

[0020] In a second aspect, compounds of Formula I having the structure according to the following Formula Ia are provided:



Formula Ia

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Y_2 is –N= and R^{15} is hydrogen; or Y_2 is-C(H)= and R^{15} is fluoro or chloro;

L_2 is $-C(H_2)-$ or -C(O)-;

Cy_2 is cycloalkyl optionally substituted with one or more R^{16}, phenyl optionally substituted with one or more R^{17}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{18} and optionally substituted on an available nitrogen atom with R^{19};

R^{14} is selected from the group consisting of cycloalkyl, lower alkyl optionally substituted with one or more R^{20}, $-N(R^{9a})(R^{9b})$, and $-O-R^{21}$;

each R^{16} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

each R^{17} is independently selected from the group consisting of fluoro, chloro, $-O-R^{22}$, $-S-R^{23}$, $-S(O_2)-R^{24}$, and lower alkyl optionally substitituted with one or more R^{25};

each R^{18} is independently selected from the group consisting of fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro; or two R^{18} bound to adjacent carbon atoms of the heteroaryl ring, taken together, form a fused cycloalkyl ring;

R^{19} is cycloalkyl, lower alkoxy, or lower alkyl optionally substituted with one or more fluoro;

R^{20} is fluoro or lower alkoxy optionally substitituted with one or more fluoro;

R^{21} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy;

each R^{22}, R^{23} and R^{24} are independently lower alkyl optionally substituted with one or more fluoro; and

each R^{25} is independently selected from the group consisting of fluoro, -OH, and lower alkoxy optionally substituted with one or more fluoro.

[0021] In some embodiments of compounds of Formula Ia, R^{14} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{14} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{14} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0022] In some embodiments of compounds of Formula Ia, further to any of the above embodiments of Formula Ia, Cy_2 is cycloalkyl optionally substituted with one or more R^{16}, phenyl optionally substituted with one or more R^{17}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{18} and optionally substituted on an available nitrogen atom with R^{19}, wherein cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and heteroaryl is pyridinyl or pyrazolyl.

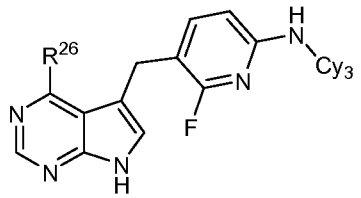
[0023] In some embodiments of compounds of Formula Ia, further to any of the above embodiments of Formula Ia, Cy_2 is cycloalkyl optionally substituted with one or more R^{16}, phenyl optionally

substituted with one or more R^{17}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{18} and optionally substituted on an available nitrogen atom with R^{19}, wherein cycloalkyl is cyclohexyl, or cycloheptyl, and heteroaryl is pyridin-3-yl or pyrazol-4-yl.

[0024] In some embodiments of compounds of Formula Ia, further to any of the above embodiments of Formula Ia, L_2 is $-C(H_2)-$. In some embodiments of compounds of Formula Ia, further to any of the above embodiments of Formula Ia, L_2 is -C(O)-.

[0025] In some embodiments of compounds of Formula Ia, further to any of the above embodiments of Formula Ia, Y_2 is –N= and R^{15} is hydrogen. In some embodiments of compounds of Formula Ia, further to any of the above embodiments of Formula Ia, Y_2 is-C(H)= and R^{15} is fluoro.

[0026] In a third aspect, compounds of Formula I having the structure according to the following Formula Ib are provided:



Formula Ib

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_3 is cycloalkyl optionally substituted with one or more R^{27}, phenyl optionally substituted with one or more R^{28}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{29} and optionally substituted on an available nitrogen atom with R^{30};

R^{26} is selected from the group consisting of cycloalkyl, lower alkyl optionally substituted with one or more R^{31}, and $-O-R^{32}$;

each R^{27} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

each R^{28} is independently selected from the group consisting of fluoro, chloro, $-O-R^{33}$, $-S-R^{34}$, $-S(O_2)-R^{35}$, and lower alkyl optionally substitituted with one or more R^{36};

each R^{29} is independently selected from the group consisting of fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro; or two R^{29} bound to adjacent carbon atoms of the heteroaryl ring, taken together, form a fused cycloalkyl ring;

R^{30} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro;

R^{31} is fluoro or lower alkoxy optionally substitituted with one or more fluoro;

R^{32} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy;

each R^{33}, R^{34} and R^{35} are independently lower alkyl optionally substituted with one or more fluoro; and

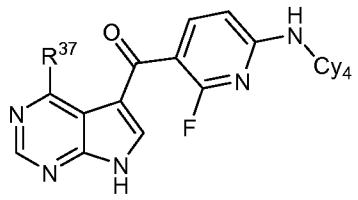
each R^{36} is independently selected from the group consisting of fluoro, -OH, and lower alkoxy optionally substituted with one or more fluoro.

[0027] In some embodiments of compounds of Formula Ib, R^{26} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{26} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{26} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0028] In some embodiments of compounds of Formula Ib, further to any of the above embodiments of Formula Ib, Cy_3 is cycloalkyl optionally substituted with one or more R^{27}, phenyl optionally substituted with one or more R^{28}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{29} and optionally substituted on an available nitrogen atom with R^{30}, wherein cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and heteroaryl is pyridinyl or pyrazolyl.

[0029] In some embodiments of compounds of Formula Ib, further to any of the above embodiments of Formula Ib, Cy_3 is cycloalkyl optionally substituted with one or more R^{27}, phenyl optionally substituted with one or more R^{28}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{29} and optionally substituted on an available nitrogen atom with R^{30}, wherein cycloalkyl is cyclohexyl, or cycloheptyl, and heteroaryl is pyridin-3-yl or pyrazol-4-yl.

[0030] In a fourth aspect, compounds of Formula I having the structure according to the following Formula Ic are provided:



Formula Ic

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_4 is cycloalkyl optionally substituted with one or more R^{38}, phenyl optionally substituted with one or more R^{39}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{40} and optionally substituted on an available nitrogen atom with R^{41};

R^{37} is selected from the group consisting of cycloalkyl, lower alkyl optionally substituted with one or more R^{42}, and -O-R^{43};

each R^{38} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

each R^{39} is independently selected from the group consisting of fluoro, chloro, -O-R^{44}, -S-R^{45}, -S(O_2)-R^{46}, and lower alkyl optionally substitituted with one or more R^{47};

each R^{40} is independently selected from the group consisting of fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro; or two R^{40} bound to adjacent carbon atoms of the heteroaryl ring, taken together, form a fused cycloalkyl ring;

R^{41} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro;

R^{42} is fluoro or lower alkoxy optionally substitituted with one or more fluoro;

R^{43} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy;

each R^{44}, R^{45} and R^{46} are independently lower alkyl optionally substituted with one or more fluoro; and

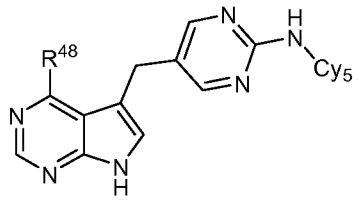
each R^{47} is independently selected from the group consisting of fluoro, -OH, and lower alkoxy optionally substituted with one or more fluoro.

[0031] In some embodiments of compounds of Formula Ic, R^{37} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{37} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{37} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0032] In some embodiments of compounds of Formula Ic, further to any of the above embodiments of Formula Ic, Cy_4 is cycloalkyl optionally substituted with one or more R^{38}, phenyl optionally substituted with one or more R^{39}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{40} and optionally substituted on an available nitrogen atom with R^{41}, wherein cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and heteroaryl is pyridinyl or pyrazolyl.

[0033] In some embodiments of compounds of Formula Ic, further to any of the above embodiments of Formula Ic, Cy_4 is cycloalkyl optionally substituted with one or more R^{38}, phenyl optionally substituted with one or more R^{39}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{40} and optionally substituted on an available nitrogen atom with R^{41}, wherein cycloalkyl is cyclohexyl, or cycloheptyl, and heteroaryl is pyridin-3-yl or pyrazol-4-yl.

[0034] In a fifth aspect, compounds of Formula I having the structure according to the following Formula Id are provided:



Formula Id

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_5 is cycloalkyl optionally substituted with one or more R^{49}, phenyl optionally substituted with one or more R^{50}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{51} and optionally substituted on an available nitrogen atom with R^{52};

R^{48} is selected from the group consisting of cycloalkyl, lower alkyl optionally substituted with one or more R^{53}, and -O-R^{54};

each R^{49} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

each R^{50} is independently selected from the group consisting of fluoro, chloro, -O-R^{55}, -S-R^{56}, -S(O_2)-R^{57}, and lower alkyl optionally substitituted with one or more R^{58};

each R^{51} is independently selected from the group consisting of fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro; or two R^{51} bound to adjacent carbon atoms of the heteroaryl ring, taken together, form a fused cycloalkyl ring;

R^{52} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro;

R^{53} is fluoro or lower alkoxy optionally substitituted with one or more fluoro;

R^{54} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy;

each R^{55}, R^{56} and R^{57} are independently lower alkyl optionally substituted with one or more fluoro; and

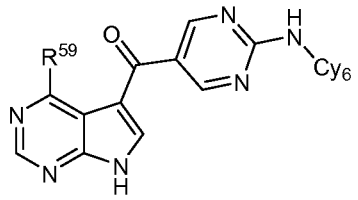
each R^{58} is independently selected from the group consisting of fluoro, -OH, and lower alkoxy optionally substituted with one or more fluoro.

[0035] In some embodiments of compounds of Formula Id, R^{48} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{48} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{48} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0036] In some embodiments of compounds of Formula Id, further to any of the above embodiments of Formula Id, Cy_5 is cycloalkyl optionally substituted with one or more R^{49}, phenyl optionally substituted with one or more R^{50}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{51} and optionally substituted on an available nitrogen atom with R^{52}, wherein cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and heteroaryl is pyridinyl or pyrazolyl.

[0037] In some embodiments of compounds of Formula Id, further to any of the above embodiments of Formula Id, Cy_5 is cycloalkyl optionally substituted with one or more R^{49}, phenyl optionally substituted with one or more R^{50}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{51} and optionally substituted on an available nitrogen atom with R^{52}, wherein cycloalkyl is cyclohexyl, or cycloheptyl, and heteroaryl is pyridin-3-yl or pyrazol-4-yl.

[0038] In a sixth aspect, compounds of Formula I having the structure according to the following Formula Ie are provided:



Formula Ie

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_6 is cycloalkyl optionally substituted with one or more R^{60}, phenyl optionally substituted with one or more R^{61}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{62} and optionally substituted on an available nitrogen atom with R^{63};

R^{59} is selected from the group consisting of cycloalkyl, lower alkyl optionally substituted with one or more R^{64}, and -O-R^{65};

each R^{60} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

each R^{61} is independently selected from the group consisting of fluoro, chloro, -O-R^{66}, -S-R^{67}, -S(O_2)-R^{68}, and lower alkyl optionally substitituted with one or more R^{69};

each R^{62} is independently selected from the group consisting of fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro; or two R^{62} bound to adjacent carbon atoms of the heteroaryl ring, taken together, form a fused cycloalkyl ring;

R^{63} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro;

R^{64} is fluoro or lower alkoxy optionally substitituted with one or more fluoro;

R^{65} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy;

each R^{66}, R^{67} and R^{68} are independently lower alkyl optionally substituted with one or more fluoro; and

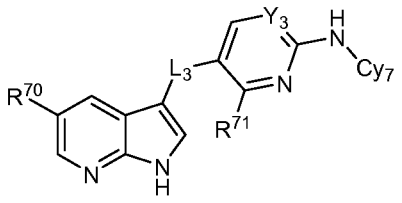
each R^{69} is independently selected from the group consisting of fluoro, -OH, and lower alkoxy optionally substituted with one or more fluoro.

[0039] In some embodiments of compounds of Formula Ie, R^{59} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{59} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{59} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0040] In some embodiments of compounds of Formula Ie, further to any of the above embodiments of Formula Ie, Cy_6 is cycloalkyl optionally substituted with one or more R^{60}, phenyl optionally substituted with one or more R^{61}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{62} and optionally substituted on an available nitrogen atom with R^{63}, wherein cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and heteroaryl is pyridinyl or pyrazolyl.

[0041] In some embodiments of compounds of Formula Ie, further to any of the above embodiments of Formula Ie, Cy_6 is cycloalkyl optionally substituted with one or more R^{60}, phenyl optionally substituted with one or more R^{61}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{62} and optionally substituted on an available nitrogen atom with R^{63}, wherein cycloalkyl is cyclohexyl, or cycloheptyl, and heteroaryl is pyridin-3-yl or pyrazol-4-yl.

[0042] In a seventh aspect, compounds of Formula I having the structure according to the following Formula If are provided:



Formula If

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Y_3 is –N= and R^{71} is hydrogen; or Y_3 is-C(H)= and R^{71} is fluoro;

L_3 is -$C(H_2)$- or -C(O)-;

Cy_7 is cycloalkyl optionally substituted with one or more R^{72}, phenyl optionally substituted with one or more R^{73}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{74} and optionally substituted on an available nitrogen atom with R^{75};

R^{70} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

each R^{72} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

each R^{73} is independently selected from the group consisting of fluoro, chloro, -O-R^{76}, -S-R^{77}, -S(O_2)-R^{78}, and lower alkyl optionally substitituted with one or more R^{79};

each R^{74} is independently selected from the group consisting of fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro; or two R^{74} bound to adjacent carbon atoms of the heteroaryl ring, taken together, form a fused cycloalkyl ring;

R^{75} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro;

each R^{76}, R^{77} and R^{78} are independently lower alkyl optionally substituted with one or more fluoro; and

each R^{79} is independently selected from the group consisting of fluoro, -OH, and lower alkoxy optionally substituted with one or more fluoro.

[0043] In some embodiments of compounds of Formula If, R^{70} is hydrogen, chloro or lower alkyl. In one embodiment, R^{70} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{70} is hydrogen, chloro or methyl.

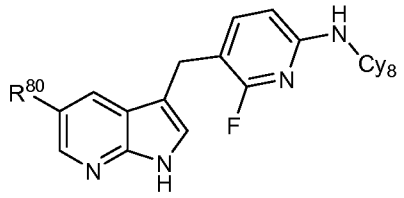
[0044] In some embodiments of compounds of Formula If, further to any of the above embodiments of Formula If, Cy_7 is cycloalkyl optionally substituted with one or more R^{72}, phenyl optionally substituted with one or more R^{73}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{74} and optionally substituted on an available nitrogen atom with R^{75}, wherein cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and heteroaryl is pyridinyl or pyrazolyl.

[0045] In some embodiments of compounds of Formula If, further to any of the above embodiments of Formula If, Cy_7 is cycloalkyl optionally substituted with one or more R^{72}, phenyl optionally substituted with one or more R^{73}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{74} and optionally substituted on an available nitrogen atom with R^{75}, wherein cycloalkyl is cyclohexyl, or cycloheptyl, and heteroaryl is pyridin-3-yl or pyrazol-4-yl.

[0046] In some embodiments of compounds of Formula If, further to any of the above embodiments of Formula If, L_3 is -C(H_2)-. In some embodiments of compounds of Formula If, further to any of the above embodiments of Formula If, L_3 is -C(O)-.

[0047] In some embodiments of compounds of Formula If, further to any of the above embodiments of Formula If, Y_3 is –N= and R^{71} is hydrogen. In some embodiments of compounds of Formula If, further to any of the above embodiments of Formula If, Y_3 is -C(H)= and R^{71} is fluoro.

[0048] In an eighth aspect, compounds of Formula I having the structure according to the following Formula Ig are provided:



Formula Ig

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_8 is cycloalkyl optionally substituted with one or more R^{81}, phenyl optionally substituted with one or more R^{82}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{83} and optionally substituted on an available nitrogen atom with R^{84};

R^{80} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

each R^{81} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

each R^{82} is independently selected from the group consisting of fluoro, chloro, -O-R^{85}, -S-R^{86}, -S(O_2)-R^{87}, and lower alkyl optionally substitituted with one or more R^{88};

each R^{83} is independently selected from the group consisting of fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro; or two R^{83} bound to adjacent carbon atoms of the heteroaryl ring, taken together, form a fused cycloalkyl ring;

R^{84} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro;

each R^{85}, R^{86} and R^{87} are independently lower alkyl optionally substituted with one or more fluoro; and

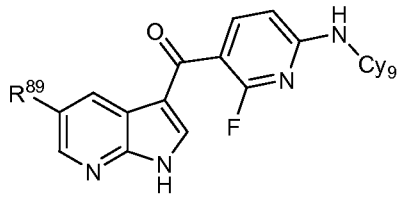
each R^{88} is independently selected from the group consisting of fluoro, -OH, and lower alkoxy optionally substituted with one or more fluoro.

[0049] In some embodiments of compounds of Formula Ig, R^{80} is hydrogen, chloro or lower alkyl. In one embodiment, R^{80} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{80} is hydrogen, chloro or methyl.

[0050] In some embodiments of compounds of Formula Ig, further to any of the above embodiments of Formula Ig, Cy_8 is cycloalkyl optionally substituted with one or more R^{81}, phenyl optionally substituted with one or more R^{82}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{83} and optionally substituted on an available nitrogen atom with R^{84}, wherein cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and heteroaryl is pyridinyl or pyrazolyl.

[0051] In some embodiments of compounds of Formula Ig, further to any of the above embodiments of Formula Ig, Cy_8 is cycloalkyl optionally substituted with one or more R^{81}, phenyl optionally substituted with one or more R^{82}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{83} and optionally substituted on an available nitrogen atom with R^{84}, wherein cycloalkyl is cyclohexyl, or cycloheptyl, and heteroaryl is pyridin-3-yl or pyrazol-4-yl.

[0052] In a ninth aspect, compounds of Formula I having the structure according to the following Formula Ih are provided:



Formula Ih

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_9 is cycloalkyl optionally substituted with one or more R^{90}, phenyl optionally substituted with one or more R^{91}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{92} and optionally substituted on an available nitrogen atom with R^{93};

R^{89} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

each R^{90} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

each R^{91} is independently selected from the group consisting of fluoro, chloro, -O-R^{94}, -S-R^{95}, -S(O_2)-R^{96}, and lower alkyl optionally substitituted with one or more R^{97};

each R^{92} is independently selected from the group consisting of fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, and lower alkoxy optionally

substituted with one or more fluoro; or two R^{92} bound to adjacent carbon atoms of the heteroaryl ring, taken together, form a fused cycloalkyl ring;

R^{93} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro;

each R^{94}, R^{95} and R^{96} are independently lower alkyl optionally substituted with one or more fluoro; and

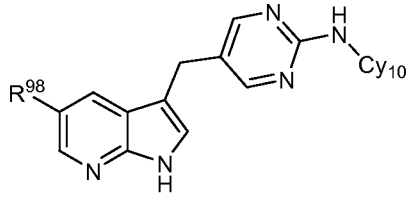
each R^{97} is independently selected from the group consisting of fluoro, -OH, and lower alkoxy optionally substituted with one or more fluoro.

[0053] In some embodiments of compounds of Formula Ih, R^{89} is hydrogen, chloro or lower alkyl. In one embodiment, R^{89} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{89} is hydrogen, chloro or methyl.

[0054] In some embodiments of compounds of Formula Ih, further to any of the above embodiments of Formula Ih, Cy_9 is cycloalkyl optionally substituted with one or more R^{90}, phenyl optionally substituted with one or more R^{91}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{92} and optionally substituted on an available nitrogen atom with R^{93}, wherein cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and heteroaryl is pyridinyl or pyrazolyl.

[0055] In some embodiments of compounds of Formula Ih, further to any of the above embodiments of Formula Ih, Cy_9 is cycloalkyl optionally substituted with one or more R^{90}, phenyl optionally substituted with one or more R^{91}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{92} and optionally substituted on an available nitrogen atom with R^{93}, wherein cycloalkyl is cyclohexyl, or cycloheptyl, and heteroaryl is pyridin-3-yl or pyrazol-4-yl.

[0056] In a tenth aspect, compounds of Formula I having the structure according to the following Formula Ii are provided:



Formula Ii

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_{10} is cycloalkyl optionally substituted with one or more R^{99}, phenyl optionally substituted with one or more R^{100}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{101} and optionally substituted on an available nitrogen atom with R^{102};

R^{98} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

each R^{99} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

each R^{100} is independently selected from the group consisting of fluoro, chloro, -O-R^{103}, -S-R^{104}, -S(O_2)-R^{105}, and lower alkyl optionally substitituted with one or more R^{106};

each R^{101} is independently selected from the group consisting of fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro; or two R^{101} bound to adjacent carbon atoms of the heteroaryl ring, taken together, form a fused cycloalkyl ring;

R^{102} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro;

each R^{102}, R^{104} and R^{105} are independently lower alkyl optionally substituted with one or more fluoro; and

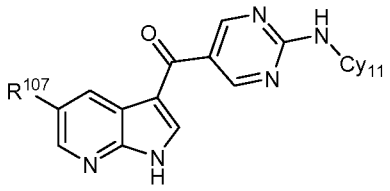
each R^{106} is independently selected from the group consisting of fluoro, -OH, and lower alkoxy optionally substituted with one or more fluoro.

[0057] In some embodiments of compounds of Formula Ii, R^{98} is hydrogen, chloro or lower alkyl. In one embodiment, R^{98} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{98} is hydrogen, chloro or methyl.

[0058] In some embodiments of compounds of Formula Ii, further to any of the above embodiments of Formula Ii, Cy_{10} is cycloalkyl optionally substituted with one or more R^{99}, phenyl optionally substituted with one or more R^{100}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{101} and optionally substituted on an available nitrogen atom with R^{102}, wherein cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and heteroaryl is pyridinyl or pyrazolyl.

[0059] In some embodiments of compounds of Formula Ii, further to any of the above embodiments of Formula Ii, Cy_{10} is cycloalkyl optionally substituted with one or more R^{99}, phenyl optionally substituted with one or more R^{100}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{101} and optionally substituted on an available nitrogen atom with R^{102}, wherein cycloalkyl is cyclohexyl, or cycloheptyl, and heteroaryl is pyridin-3-yl or pyrazol-4-yl.

[0060] In an eleventh aspect, compounds of Formula I having the structure according to the following Formula Ij are provided:



Formula Ij

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_{11} is cycloalkyl optionally substituted with one or more R^{108}, phenyl optionally substituted with one or more R^{109}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{110} and optionally substituted on an available nitrogen atom with R^{111};

R^{107} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

each R^{108} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

each R^{109} is independently selected from the group consisting of fluoro, chloro, -O-R^{112}, -S-R^{113}, -S(O_2)-R^{114}, and lower alkyl optionally substitituted with one or more R^{115};

each R^{110} is independently selected from the group consisting of fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro; or two R^{110} bound to adjacent carbon atoms of the heteroaryl ring, taken together, form a fused cycloalkyl ring;

R^{111} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro;

each R^{112}, R^{113} and R^{114} are independently lower alkyl optionally substituted with one or more fluoro; and

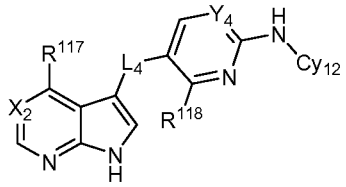
each R^{115} is independently selected from the group consisting of fluoro, -OH, and lower alkoxy optionally substituted with one or more fluoro.

[0061] In some embodiments of compounds of Formula Ij, R^{107} is hydrogen, chloro or lower alkyl. In one embodiment, R^{107} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{107} is hydrogen, chloro or methyl.

[0062] In some embodiments of compounds of Formula Ij, further to any of the above embodiments of Formula Ij, Cy_{11} is cycloalkyl optionally substituted with one or more R^{108}, phenyl optionally substituted with one or more R^{109}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{110} and optionally substituted on an available nitrogen atom with R^{111}, wherein cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and heteroaryl is pyridinyl or pyrazolyl.

[0063] In some embodiments of compounds of Formula Ij, further to any of the above embodiments of Formula Ij, Cy_{11} is cycloalkyl optionally substituted with one or more R^{108}, phenyl optionally substituted with one or more R^{109}, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^{110} and optionally substituted on an available nitrogen atom with R^{111}, wherein cycloalkyl is cyclohexyl, or cycloheptyl, and heteroaryl is pyridin-3-yl or pyrazol-4-yl.

[0064] In a twelfth aspect, compounds of Formula I having the structure according to the following Formula Ik are provided:



Formula Ik

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

X_2 is –N=, -C(H)=, or -C(R^{116})= ;

Y_4 is –N= and R^{118} is hydrogen; or Y_4 is-C(H)= and R^{118} is fluoro;

L_4 is -C(H_2)- or -C(O)-;

Cy_{12} is cycloalkyl optionally substituted with one or more R^{119};

when X_2 is -C(R^{116})=, R^{117} is hydrogen;

when X_2 is –N= or -C(H)=, R^{117} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{120}, and -O-R^{121};

R^{116} is fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

each R^{119} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

R^{120} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{121} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0065] In some embodiments of compounds of Formula Ik, X_2 is –N= and R^{117} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{120}, and -O-R^{121}. In one embodiment, X_2 is –N= and R^{117} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, X_2 is –N= and R^{117} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl,

C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, X_2 is -N= and R^{117} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0066] In some embodiments of compounds of Formula Ik, X_2 is -C(H)= or -C(R^{116})= and R^{116} is fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro. In one embodiment, X_2 is -C(H)= or -C(R^{116})= and R^{116} is chloro or lower alkyl. In one embodiment, X_2 is -C(H)= or -C(R^{116})= and R^{116} is chloro or C_{1-3} alkyl. In one embodiment, X_2 is -C(H)= or -C(R^{116})= and R^{116} is chloro or methyl.

[0067] In some embodiments of compounds of Formula Ik, further to any of the above embodiments of Formula Ik, Cy_{12} is cyclopentyl optionally substituted with 1 or 2 R^{119}, cyclohexyl optionally substituted with 1 or 2 R^{119}, or cycloheptyl optionally substituted with 1 or 2 R^{119}.

[0068] In some embodiments of compounds of Formula Ik, further to any of the above embodiments of Formula Ik, Cy_{12} is cyclopentyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; cyclohexyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; or cycloheptyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy.

[0069] In some embodiments of compounds of Formula Ik, further to any of the above embodiments of Formula Ik, Cy_{12} is cyclopentyl, cyclopentyl substituted with 1 or 2 fluoro, cyclopentyl substituted with 1 or 2 lower alkyl, cyclopentyl substituted with 1 or 2 -OH, or cyclopentyl substituted with 1 or 2 lower alkoxy.

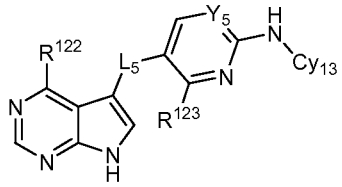
[0070] In some embodiments of compounds of Formula Ik, further to any of the above embodiments of Formula Ik, Cy_{12} is cyclohexyl, cyclohexyl substituted with 1 or 2 fluoro, cyclohexyl substituted with 1 or 2 lower alkyl, cyclohexyl substituted with 1 or 2 -OH, or cyclohexyl substituted with 1 or 2 lower alkoxy.

[0071] In some embodiments of compounds of Formula Ik, further to any of the above embodiments of Formula Ik, Cy_{12} is cycloheptyl, cycloheptyl substituted with 1 or 2 fluoro, cycloheptyl substituted with 1 or 2 lower alkyl, cycloheptyl substituted with 1 or 2 -OH, or cycloheptyl substituted with 1 or 2 lower alkoxy.

[0072] In some embodiments of compounds of Formula Ik, further to any of the above embodiments of Formula Ik, L_4 is -C(H_2)-. In some embodiments of compounds of Formula Ik, further to any of the above embodiments of Formula Ik, L_4 is -C(O)-.

[0073] In some embodiments of compounds of Formula Ik, further to any of the above embodiments of Formula Ik, Y_4 is –N= and R^{118} is hydrogen. In some embodiments of compounds of Formula Ik, further to any of the above embodiments of Formula Ik, Y_4 is-C(H)= and R^{118} is fluoro.

[0074] In a thirteenth aspect, compounds of Formula I having the structure according to the following Formula Im are provided:



Formula Im

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Y_5 is –N= and R^{123} is hydrogen; or Y_5 is-C(H)= and R^{123} is fluoro;

L_5 is -C(H_2)- or -C(O)-;

Cy_{13} is cycloalkyl optionally substituted with one or more R^{124};

R^{122} is selected from the group consisting of cycloalkyl, lower alkyl optionally substituted with one or more R^{125}, and -O-R^{126};

each R^{124} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

R^{125} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{126} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0075] In some embodiments of compounds of Formula Im, R^{122} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment R^{122} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment R^{122} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0076] In some embodiments of compounds of Formula Im, further to any of the above embodiments of Formula Im, Cy_{13} is cyclopentyl optionally substituted with 1 or 2 R^{124}, cyclohexyl optionally substituted with 1 or 2 R^{124}, or cycloheptyl optionally substituted with 1 or 2 R^{124}.

[0077] In some embodiments of compounds of Formula Im, further to any of the above embodiments of Formula Im, Cy_{13} is cyclopentyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; cyclohexyl optionally substituted with 1 or 2

fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; or cycloheptyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy.

[0078] In some embodiments of compounds of Formula Im, further to any of the above embodiments of Formula Im, Cy_{13} is cyclopentyl, cyclopentyl substituted with 1 or 2 fluoro, cyclopentyl substituted with 1 or 2 lower alkyl, cyclopentyl substituted with 1 or 2 -OH, or cyclopentyl substituted with 1 or 2 lower alkoxy.

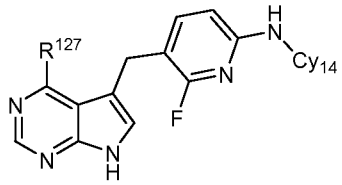
[0079] In some embodiments of compounds of Formula Im, further to any of the above embodiments of Formula Im, Cy_{13} is cyclohexyl, cyclohexyl substituted with 1 or 2 fluoro, cyclohexyl substituted with 1 or 2 lower alkyl, cyclohexyl substituted with 1 or 2 -OH, or cyclohexyl substituted with 1 or 2 lower alkoxy.

[0080] In some embodiments of compounds of Formula Im, further to any of the above embodiments of Formula Im, Cy_{13} is cycloheptyl, cycloheptyl substituted with 1 or 2 fluoro, cycloheptyl substituted with 1 or 2 lower alkyl, cycloheptyl substituted with 1 or 2 -OH, or cycloheptyl substituted with 1 or 2 lower alkoxy.

[0081] In some embodiments of compounds of Formula Im, further to any of the above embodiments of Formula Im, L_5 is $-C(H_2)-$. In some embodiments of compounds of Formula Im, further to any of the above embodiments of Formula Im, L_5 is -C(O)-.

[0082] In some embodiments of compounds of Formula Im, further to any of the above embodiments of Formula Im, Y_5 is –N= and R^{123} is hydrogen. In some embodiments of compounds of Formula Im, further to any of the above embodiments of Formula Im, Y_5 is -C(H)= and R^{123} is fluoro.

[0083] In a fourteenth aspect, compounds of Formula I having the structure according to the following Formula In are provided:



Formula In

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_{14} is cycloalkyl optionally substituted with one or more R^{128};

R^{127} is selected from the group consisting of cycloalkyl, lower alkyl optionally substituted with one or more R^{129}, and -O-R^{130};

each R^{128} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

R^{129} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{130} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0084] In some embodiments of compounds of Formula In, R^{127} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment R^{127} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment R^{127} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0085] In some embodiments of compounds of Formula In, further to any of the above embodiments of Formula In, Cy_{14} is cyclopentyl optionally substituted with 1 or 2 R^{128}, cyclohexyl optionally substituted with 1 or 2 R^{128}, or cycloheptyl optionally substituted with 1 or 2 R^{128}.

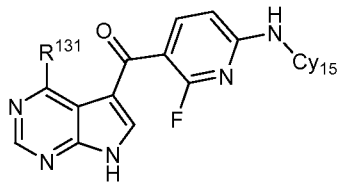
[0086] In some embodiments of compounds of Formula In, further to any of the above embodiments of Formula In, Cy_{14} is cyclopentyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; cyclohexyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; or cycloheptyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy.

[0087] In some embodiments of compounds of Formula In, further to any of the above embodiments of Formula In, Cy_{14} is cyclopentyl, cyclopentyl substituted with 1 or 2 fluoro, cyclopentyl substituted with 1 or 2 lower alkyl, cyclopentyl substituted with 1 or 2 -OH, or cyclopentyl substituted with 1 or 2 lower alkoxy.

[0088] In some embodiments of compounds of Formula In, further to any of the above embodiments of Formula In, Cy_{14} is cyclohexyl, cyclohexyl substituted with 1 or 2 fluoro, cyclohexyl substituted with 1 or 2 lower alkyl, cyclohexyl substituted with 1 or 2 -OH, or cyclohexyl substituted with 1 or 2 lower alkoxy.

[0089] In some embodiments of compounds of Formula In, further to any of the above embodiments of Formula In, Cy_{14} is cycloheptyl, cycloheptyl substituted with 1 or 2 fluoro, cycloheptyl substituted with 1 or 2 lower alkyl, cycloheptyl substituted with 1 or 2 -OH, or cycloheptyl substituted with 1 or 2 lower alkoxy.

[0090] In a fifteenth aspect, compounds of Formula I having the structure according to the following Formula Io are provided:



Formula Io

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_{15} is cycloalkyl optionally substituted with one or more R^{132};

R^{131} is selected from the group consisting of cycloalkyl, lower alkyl optionally substituted with one or more R^{133}, and -O-R^{134};

each R^{132} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

R^{133} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{134} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0091] In some embodiments of compounds of Formula Io, R^{131} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment R^{131} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment R^{131} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0092] In some embodiments of compounds of Formula Io, further to any of the above embodiments of Formula Io, Cy_{15} is cyclopentyl optionally substituted with 1 or 2 R^{132}, cyclohexyl optionally substituted with 1 or 2 R^{132}, or cycloheptyl optionally substituted with 1 or 2 R^{132}.

[0093] In some embodiments of compounds of Formula Io, further to any of the above embodiments of Formula Io, Cy_{15} is cyclopentyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; cyclohexyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; or cycloheptyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy.

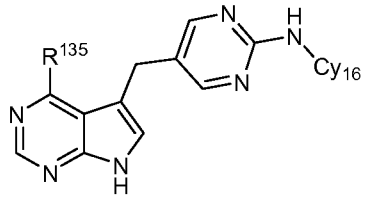
[0094] In some embodiments of compounds of Formula Io, further to any of the above embodiments of Formula Io, Cy_{15} is cyclopentyl, cyclopentyl substituted with 1 or 2 fluoro, cyclopentyl substituted

with 1 or 2 lower alkyl, cyclopentyl substituted with 1 or 2 -OH, or cyclopentyl substituted with 1 or 2 lower alkoxy.

[0095] In some embodiments of compounds of Formula Io, further to any of the above embodiments of Formula Io, Cy_{15} is cyclohexyl, cyclohexyl substituted with 1 or 2 fluoro, cyclohexyl substituted with 1 or 2 lower alkyl, cyclohexyl substituted with 1 or 2 -OH, or cyclohexyl substituted with 1 or 2 lower alkoxy.

[0096] In some embodiments of compounds of Formula Io, further to any of the above embodiments of Formula Io, Cy_{15} is cycloheptyl, cycloheptyl substituted with 1 or 2 fluoro, cycloheptyl substituted with 1 or 2 lower alkyl, cycloheptyl substituted with 1 or 2 -OH, or cycloheptyl substituted with 1 or 2 lower alkoxy.

[0097] In a sixteenth aspect, compounds of Formula I having the structure according to the following Formula Ip are provided:



Formula Ip

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_{16} is cycloalkyl optionally substituted with one or more R^{136};

R^{135} is selected from the group consisting of cycloalkyl, lower alkyl optionally substituted with one or more R^{137}, and -O-R^{138};

each R^{136} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

R^{137} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{138} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0098] In some embodiments of compounds of Formula Ip, R^{135} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment R^{135} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment R^{135} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0099] In some embodiments of compounds of Formula Ip, further to any of the above embodiments of Formula Ip, Cy_{16} is cyclopentyl optionally substituted with 1 or 2 R^{136}, cyclohexyl optionally substituted with 1 or 2 R^{136}, or cycloheptyl optionally substituted with 1 or 2 R^{136}.

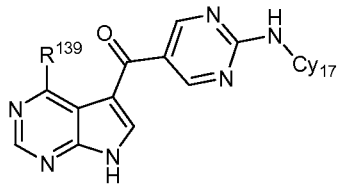
[0100] In some embodiments of compounds of Formula Ip, further to any of the above embodiments of Formula Ip, Cy_{16} is cyclopentyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; cyclohexyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; or cycloheptyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy.

[0101] In some embodiments of compounds of Formula Ip, further to any of the above embodiments of Formula Ip, Cy_{16} is cyclopentyl, cyclopentyl substituted with 1 or 2 fluoro, cyclopentyl substituted with 1 or 2 lower alkyl, cyclopentyl substituted with 1 or 2 -OH, or cyclopentyl substituted with 1 or 2 lower alkoxy.

[0102] In some embodiments of compounds of Formula Ip, further to any of the above embodiments of Formula Ip, Cy_{16} is cyclohexyl, cyclohexyl substituted with 1 or 2 fluoro, cyclohexyl substituted with 1 or 2 lower alkyl, cyclohexyl substituted with 1 or 2 -OH, or cyclohexyl substituted with 1 or 2 lower alkoxy.

[0103] In some embodiments of compounds of Formula Ip, further to any of the above embodiments of Formula Ip, Cy_{16} is cycloheptyl, cycloheptyl substituted with 1 or 2 fluoro, cycloheptyl substituted with 1 or 2 lower alkyl, cycloheptyl substituted with 1 or 2 -OH, or cycloheptyl substituted with 1 or 2 lower alkoxy.

[0104] In a seventeenth aspect, compounds of Formula I having the structure according to the following Formula Iq are provided:



Formula Iq

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_{16} is cycloalkyl optionally substituted with one or more R^{140};

R^{139} is selected from the group consisting of cycloalkyl, lower alkyl optionally substituted with one or more R^{141}, and -O-R^{142};

each R^{140} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

R^{141} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{142} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0105] In some embodiments of compounds of Formula Iq, R^{139} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment R^{139} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment R^{139} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0106] In some embodiments of compounds of Formula Iq, further to any of the above embodiments of Formula Iq, Cy_{17} is cyclopentyl optionally substituted with 1 or 2 R^{140}, cyclohexyl optionally substituted with 1 or 2 R^{140}, or cycloheptyl optionally substituted with 1 or 2 R^{140}.

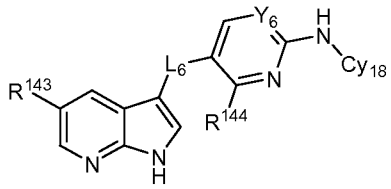
[0107] In some embodiments of compounds of Formula Iq, further to any of the above embodiments of Formula Iq, Cy_{17} is cyclopentyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; cyclohexyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; or cycloheptyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy.

[0108] In some embodiments of compounds of Formula Iq, further to any of the above embodiments of Formula Iq, Cy_{17} is cyclopentyl, cyclopentyl substituted with 1 or 2 fluoro, cyclopentyl substituted with 1 or 2 lower alkyl, cyclopentyl substituted with 1 or 2 -OH, or cyclopentyl substituted with 1 or 2 lower alkoxy.

[0109] In some embodiments of compounds of Formula Iq, further to any of the above embodiments of Formula Iq, Cy_{17} is cyclohexyl, cyclohexyl substituted with 1 or 2 fluoro, cyclohexyl substituted with 1 or 2 lower alkyl, cyclohexyl substituted with 1 or 2 -OH, or cyclohexyl substituted with 1 or 2 lower alkoxy.

[0110] In some embodiments of compounds of Formula Iq, further to any of the above embodiments of Formula Iq, Cy_{17} is cycloheptyl, cycloheptyl substituted with 1 or 2 fluoro, cycloheptyl substituted with 1 or 2 lower alkyl, cycloheptyl substituted with 1 or 2 -OH, or cycloheptyl substituted with 1 or 2 lower alkoxy.

[0111] In an eighteenth aspect, compounds of Formula I having the structure according to the following Formula Ir are provided:



Formula Ir

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Y_6 is –N= and R^{144} is hydrogen; or Y_6 is-C(H)= and R^{144} is fluoro;

L_6 is -C(H_2)- or -C(O)-;

Cy_{18} is cycloalkyl optionally substituted with one or more R^{145};

R^{143} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro; and

each R^{145} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro.

[0112] In some embodiments of compounds of Formula Ir, R^{143} is hydrogen, chloro or lower alkyl. In one embodiment, R^{143} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{143} is hydrogen, chloro or methyl.

[0113] In some embodiments of compounds of Formula Ir, further to any of the above embodiments of Formula Ir, Cy_{18} is cyclopentyl optionally substituted with 1 or 2 R^{145}, cyclohexyl optionally substituted with 1 or 2 R^{145}, or cycloheptyl optionally substituted with 1 or 2 R^{145}.

[0114] In some embodiments of compounds of Formula Ir, further to any of the above embodiments of Formula Ir, Cy_{18} is cyclopentyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; cyclohexyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; or cycloheptyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy.

[0115] In some embodiments of compounds of Formula Ir, further to any of the above embodiments of Formula Ir, Cy_{18} is cyclopentyl, cyclopentyl substituted with 1 or 2 fluoro, cyclopentyl substituted with 1 or 2 lower alkyl, cyclopentyl substituted with 1 or 2 -OH, or cyclopentyl substituted with 1 or 2 lower alkoxy.

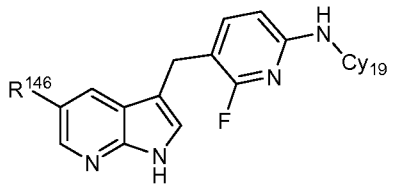
[0116] In some embodiments of compounds of Formula Ir, further to any of the above embodiments of Formula Ir, Cy_{18} is cyclohexyl, cyclohexyl substituted with 1 or 2 fluoro, cyclohexyl substituted with 1 or 2 lower alkyl, cyclohexyl substituted with 1 or 2 -OH, or cyclohexyl substituted with 1 or 2 lower alkoxy.

[0117] In some embodiments of compounds of Formula Ir, further to any of the above embodiments of Formula Ir, Cy_{18} is cycloheptyl, cycloheptyl substituted with 1 or 2 fluoro, cycloheptyl substituted with 1 or 2 lower alkyl, cycloheptyl substituted with 1 or 2 -OH, or cycloheptyl substituted with 1 or 2 lower alkoxy.

[0118] In some embodiments of compounds of Formula Ir, further to any of the above embodiments of Formula Ir, L_6 is $-C(H_2)-$. In some embodiments of compounds of Formula Ir, further to any of the above embodiments of Formula Ir, L_6 is -C(O)-.

[0119] In some embodiments of compounds of Formula Ir, further to any of the above embodiments of Formula Ir, Y_6 is –N= and R^{144} is hydrogen. In some embodiments of compounds of Formula Ir, further to any of the above embodiments of Formula Ir, Y_6 is-C(H)= and R^{144} is fluoro.

[0120] In a nineteenth aspect, compounds of Formula I having the structure according to the following Formula Is are provided:



Formula Is

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_{19} is cycloalkyl optionally substituted with one or more R^{147};

R^{146} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro; and

each R^{147} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro.

[0121] In some embodiments of compounds of Formula Is, R^{146} is hydrogen, chloro or lower alkyl. In one embodiment, R^{146} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{146} is hydrogen, chloro or methyl.

[0122] In some embodiments of compounds of Formula Is, further to any of the above embodiments of Formula Is, Cy_{19} is cyclopentyl optionally substituted with 1 or 2 R^{147}, cyclohexyl optionally substituted with 1 or 2 R^{147}, or cycloheptyl optionally substituted with 1 or 2 R^{147}.

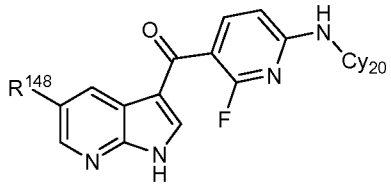
[0123] In some embodiments of compounds of Formula Is, further to any of the above embodiments of Formula Is, Cy_{19} is cyclopentyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; cyclohexyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; or cycloheptyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy.

[0124] In some embodiments of compounds of Formula Is, further to any of the above embodiments of Formula Is, Cy_{19} is cyclopentyl, cyclopentyl substituted with 1 or 2 fluoro, cyclopentyl substituted with 1 or 2 lower alkyl, cyclopentyl substituted with 1 or 2 -OH, or cyclopentyl substituted with 1 or 2 lower alkoxy.

[0125] In some embodiments of compounds of Formula Is, further to any of the above embodiments of Formula Is, Cy_{19} is cyclohexyl, cyclohexyl substituted with 1 or 2 fluoro, cyclohexyl substituted with 1 or 2 lower alkyl, cyclohexyl substituted with 1 or 2 -OH, or cyclohexyl substituted with 1 or 2 lower alkoxy.

[0126] In some embodiments of compounds of Formula Is, further to any of the above embodiments of Formula Is, Cy_{19} is cycloheptyl, cycloheptyl substituted with 1 or 2 fluoro, cycloheptyl substituted with 1 or 2 lower alkyl, cycloheptyl substituted with 1 or 2 -OH, or cycloheptyl substituted with 1 or 2 lower alkoxy.

[0127] In a twentieth aspect, compounds of Formula I having the structure according to the following Formula It are provided:



Formula It

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_{20} is cycloalkyl optionally substituted with one or more R^{149};

R^{148} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro; and

each R^{149} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro.

[0128] In some embodiments of compounds of Formula It, R^{148} is hydrogen, chloro or lower alkyl. In one embodiment, R^{148} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{148} is hydrogen, chloro or methyl.

[0129] In some embodiments of compounds of Formula It, further to any of the above embodiments of Formula It, Cy_{20} is cyclopentyl optionally substituted with 1 or 2 R^{149}, cyclohexyl optionally substituted with 1 or 2 R^{149}, or cycloheptyl optionally substituted with 1 or 2 R^{149}.

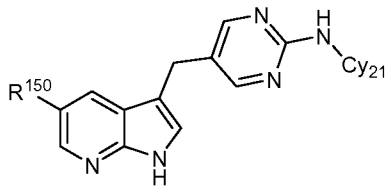
[0130] In some embodiments of compounds of Formula It, further to any of the above embodiments of Formula It, Cy_{20} is cyclopentyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; cyclohexyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; or cycloheptyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy.

[0131] In some embodiments of compounds of Formula It, further to any of the above embodiments of Formula It, Cy_{20} is cyclopentyl, cyclopentyl substituted with 1 or 2 fluoro, cyclopentyl substituted with 1 or 2 lower alkyl, cyclopentyl substituted with 1 or 2 -OH, or cyclopentyl substituted with 1 or 2 lower alkoxy.

[0132] In some embodiments of compounds of Formula It, further to any of the above embodiments of Formula It, Cy_{20} is cyclohexyl, cyclohexyl substituted with 1 or 2 fluoro, cyclohexyl substituted with 1 or 2 lower alkyl, cyclohexyl substituted with 1 or 2 -OH, or cyclohexyl substituted with 1 or 2 lower alkoxy.

[0133] In some embodiments of compounds of Formula It, further to any of the above embodiments of Formula It, Cy_{20} is cycloheptyl, cycloheptyl substituted with 1 or 2 fluoro, cycloheptyl substituted with 1 or 2 lower alkyl, cycloheptyl substituted with 1 or 2 -OH, or cycloheptyl substituted with 1 or 2 lower alkoxy.

[0134] In a twenty-first aspect, compounds of Formula I having the structure according to the following Formula Iu are provided:



Formula Iu

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_{21} is cycloalkyl optionally substituted with one or more R^{151};

R^{150} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro; and

each R^{151} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro.

[0135] In some embodiments of compounds of Formula Iu, R^{150} is hydrogen, chloro or lower alkyl. In one embodiment, R^{150} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{150} is hydrogen, chloro or methyl.

[0136] In some embodiments of compounds of Formula Iu, further to any of the above embodiments of Formula Iu, Cy_{21} is cyclopentyl optionally substituted with 1 or 2 R^{151}, cyclohexyl optionally substituted with 1 or 2 R^{151}, or cycloheptyl optionally substituted with 1 or 2 R^{151}.

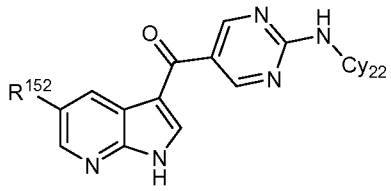
[0137] In some embodiments of compounds of Formula Iu, further to any of the above embodiments of Formula Iu, Cy_{21} is cyclopentyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; cyclohexyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; or cycloheptyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy.

[0138] In some embodiments of compounds of Formula Iu, further to any of the above embodiments of Formula Iu, Cy_{21} is cyclopentyl, cyclopentyl substituted with 1 or 2 fluoro, cyclopentyl substituted with 1 or 2 lower alkyl, cyclopentyl substituted with 1 or 2 -OH, or cyclopentyl substituted with 1 or 2 lower alkoxy.

[0139] In some embodiments of compounds of Formula Iu, further to any of the above embodiments of Formula Iu, Cy_{21} is cyclohexyl, cyclohexyl substituted with 1 or 2 fluoro, cyclohexyl substituted with 1 or 2 lower alkyl, cyclohexyl substituted with 1 or 2 -OH, or cyclohexyl substituted with 1 or 2 lower alkoxy.

[0140] In some embodiments of compounds of Formula Iu, further to any of the above embodiments of Formula Iu, Cy_{21} is cycloheptyl, cycloheptyl substituted with 1 or 2 fluoro, cycloheptyl substituted with 1 or 2 lower alkyl, cycloheptyl substituted with 1 or 2 -OH, or cycloheptyl substituted with 1 or 2 lower alkoxy.

[0141] In a twenty-second aspect, compounds of Formula I having the structure according to the following Formula Iv are provided:



Formula Iv

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Cy_{22} is cycloalkyl optionally substituted with one or more R^{153};

R^{152} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro; and

each R^{153} is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro.

[0142] In some embodiments of compounds of Formula Iv, R^{152} is hydrogen, chloro or lower alkyl. In one embodiment, R^{152} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{152} is hydrogen, chloro or methyl.

[0143] In some embodiments of compounds of Formula Iv, further to any of the above embodiments of Formula Iv, Cy_{22} is cyclopentyl optionally substituted with 1 or 2 R^{153}, cyclohexyl optionally substituted with 1 or 2 R^{153}, or cycloheptyl optionally substituted with 1 or 2 R^{153}.

[0144] In some embodiments of compounds of Formula Iv, further to any of the above embodiments of Formula Iv, Cy_{22} is cyclopentyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; cyclohexyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy; or cycloheptyl optionally substituted with 1 or 2 fluoro, or 1or 2 lower alkyl, or 1 or 2 -OH, or 1 or 2 lower alkoxy.

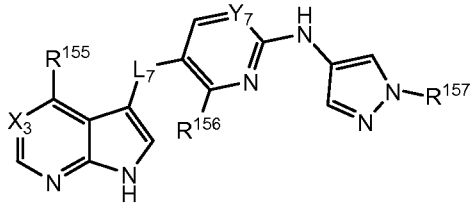
[0145] In some embodiments of compounds of Formula Iv, further to any of the above embodiments of Formula Iv, Cy_{22} is cyclopentyl, cyclopentyl substituted with 1 or 2 fluoro, cyclopentyl substituted with 1 or 2 lower alkyl, cyclopentyl substituted with 1 or 2 -OH, or cyclopentyl substituted with 1 or 2 lower alkoxy.

[0146] In some embodiments of compounds of Formula Iv, further to any of the above embodiments of Formula Iv, Cy_{22} is cyclohexyl, cyclohexyl substituted with 1 or 2 fluoro, cyclohexyl substituted

with 1 or 2 lower alkyl, cyclohexyl substituted with 1 or 2 -OH, or cyclohexyl substituted with 1 or 2 lower alkoxy.

[0147] In some embodiments of compounds of Formula Iv, further to any of the above embodiments of Formula Iv, Cy_{22} is cycloheptyl, cycloheptyl substituted with 1 or 2 fluoro, cycloheptyl substituted with 1 or 2 lower alkyl, cycloheptyl substituted with 1 or 2 -OH, or cycloheptyl substituted with 1 or 2 lower alkoxy.

[0148] In a twenty-third aspect, compounds of Formula I having the structure according to the following Formula Iw are provided:



Formula Iw

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

X_3 is –N=, -C(H)=, or -C(R^{154})= ;

Y_7 is –N= and R^{156} is hydrogen; or Y_7 is -C(H)= and R^{156} is fluoro;

L_7 is -C(H_2)- or -C(O)-;

when X_3 is -C(R^{154})=, R^{155} is hydrogen;

when X_3 is –N= or -C(H)=, R^{155} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{158}, and -O-R^{159};

R^{154} is fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

R^{157} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro;

R^{158} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{159} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0149] In some embodiments of compounds of Formula Iw, X_3 is –N= and R^{155} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{158}, and -O-R^{159}. In one embodiment, X_3 is –N= and R^{155} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, X_3 is –N= and R^{155} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, X_3 is -N= and R^{155} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0150] In some embodiments of compounds of Formula Iw, X_3 is -C(H)= or -C(R^{154})= and R^{154} is fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro. In one embodiment, X_3 is -C(H)= or -C(R^{154})= and R^{154} is chloro or lower alkyl. In one embodiment, X_3 is -C(H)= or -C(R^{154})= and R^{154} is chloro or C_{1-3} alkyl. In one embodiment, X_3 is -C(H)= or -C(R^{154})= and R^{154} is chloro or methyl.

[0151] In some embodiments of compounds of Formula Iw, further to any of the above embodiments of Formula Iw, R^{157} is cycloalkyl or lower alkyl.

[0152] In some embodiments of compounds of Formula Iw, further to any of the above embodiments of Formula Iw, R^{157} is C_{3-6} cycloalkyl or lower alkyl.

[0153] In some embodiments of compounds of Formula Iw, further to any of the above embodiments of Formula Iw, R^{157} is cyclopropyl or lower alkyl.

[0154] In some embodiments of compounds of Formula Iw, further to any of the above embodiments of Formula Iw, R^{157} is lower alkyl.

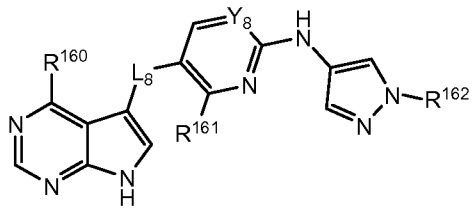
[0155] In some embodiments of compounds of Formula Iw, further to any of the above embodiments of Formula Iw, R^{157} is C_{1-3} alkyl.

[0156] In some embodiments of compounds of Formula Iw, further to any of the above embodiments of Formula Iw, R^{157} is ethyl.

[0157] In some embodiments of compounds of Formula Iw, further to any of the above embodiments of Formula Iw, L_7 is -C(H_2)-. In some embodiments of compounds of Formula Iw, further to any of the above embodiments of Formula Iw, L_7 is -C(O)-.

[0158] In some embodiments of compounds of Formula Iw, further to any of the above embodiments of Formula Iw, Y_7 is –N= and R^{156} is hydrogen. In some embodiments of compounds of Formula Iw, further to any of the above embodiments of Formula Iw, Y_7 is-C(H)= and R^{156} is fluoro.

[0159] In a twenty-fourth aspect, compounds of Formula I having the structure according to the following Formula Ix are provided:



Formula Ix

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Y_8 is –N= and R^{161} is hydrogen; or Y_8 is-C(H)= and R^{161} is fluoro;

L_8 is -$C(H_2)$- or -C(O)-;

R^{160} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{163}, and -O-R^{164};

R^{162} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro;

R^{163} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{164} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0160] In some embodiments of compounds of Formula Ix, R^{160} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{160} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{160} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0161] In some embodiments of compounds of Formula Ix, further to any of the above embodiments of Formula Ix, R^{162} is cycloalkyl or lower alkyl.

[0162] In some embodiments of compounds of Formula Ix, further to any of the above embodiments of Formula Ix, R^{162} is C_{3-6} cycloalkyl or lower alkyl.

[0163] In some embodiments of compounds of Formula Ix, further to any of the above embodiments of Formula Ix, R^{162} is cyclopropyl or lower alkyl.

[0164] In some embodiments of compounds of Formula Ix, further to any of the above embodiments of Formula Ix, R^{162} is lower alkyl.

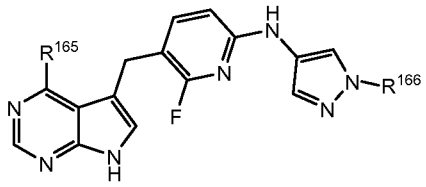
[0165] In some embodiments of compounds of Formula Ix, further to any of the above embodiments of Formula Ix, R^{162} is C_{1-3} alkyl.

[0166] In some embodiments of compounds of Formula Ix, further to any of the above embodiments of Formula Ix, R^{162} is ethyl.

[0167] In some embodiments of compounds of Formula Ix, further to any of the above embodiments of Formula Ix, L_8 is -$C(H_2)$-. In some embodiments of compounds of Formula Ix, further to any of the above embodiments of Formula Ix, L_8 is -C(O)-.

[0168] In some embodiments of compounds of Formula Ix, further to any of the above embodiments of Formula Ix, Y_8 is –N= and R^{161} is hydrogen. In some embodiments of compounds of Formula Ix, further to any of the above embodiments of Formula Ix, Y_8 is-C(H)= and R^{161} is fluoro.

[0169] In a twenty-fifth aspect, compounds of Formula I having the structure according to the following Formula Iy are provided:



Formula Iy

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{165} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{167}, and -O-R^{168};

R^{166} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro;

R^{167} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{168} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0170] In some embodiments of compounds of Formula Iy, R^{165} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{165} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{165} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0171] In some embodiments of compounds of Formula Iy, further to any of the above embodiments of Formula Iy, R^{166} is cycloalkyl or lower alkyl.

[0172] In some embodiments of compounds of Formula Iy, further to any of the above embodiments of Formula Iy, R^{166} is C_{3-6} cycloalkyl or lower alkyl.

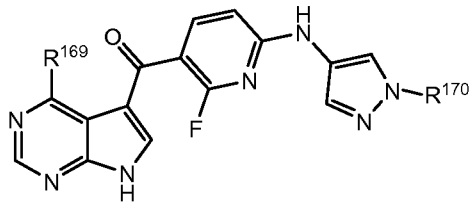
[0173] In some embodiments of compounds of Formula Iy, further to any of the above embodiments of Formula Iy, R^{166} is cyclopropyl or lower alkyl.

[0174] In some embodiments of compounds of Formula Iy, further to any of the above embodiments of Formula Iy, R^{166} is lower alkyl.

[0175] In some embodiments of compounds of Formula Iy, further to any of the above embodiments of Formula Iy, R^{166} is C_{1-3} alkyl.

[0176] In some embodiments of compounds of Formula Iy, further to any of the above embodiments of Formula Iy, R^{166} is ethyl.

[0177] In a twenty-sixth aspect, compounds of Formula I having the structure according to the following Formula Iz are provided:



Formula Iz

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{169} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{171}, and -O-R^{172};

R^{170} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro;

R^{171} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{172} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0178] In some embodiments of compounds of Formula Iz, R^{169} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{169} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{169} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0179] In some embodiments of compounds of Formula Iz, further to any of the above embodiments of Formula Iz, R^{170} is cycloalkyl or lower alkyl.

[0180] In some embodiments of compounds of Formula Iz, further to any of the above embodiments of Formula Iz, R^{170} is C_{3-6} cycloalkyl or lower alkyl.

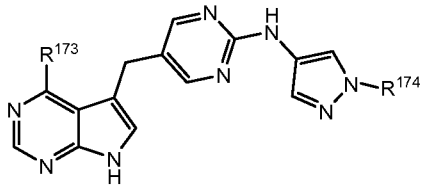
[0181] In some embodiments of compounds of Formula Iz, further to any of the above embodiments of Formula Iz, R^{170} is cyclopropyl or lower alkyl.

[0182] In some embodiments of compounds of Formula Iz, further to any of the above embodiments of Formula Iz, R^{170} is lower alkyl.

[0183] In some embodiments of compounds of Formula Iz, further to any of the above embodiments of Formula Iz, R^{170} is C_{1-3} alkyl.

[0184] In some embodiments of compounds of Formula Iz, further to any of the above embodiments of Formula Iz, R^{170} is ethyl.

[0185] In a twenty-seventh aspect, compounds of Formula I having the structure according to the following Formula Iaa are provided:



Formula Iaa

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{173} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{175}, and -O-R^{176};

R^{174} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro;

R^{175} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{176} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0186] In some embodiments of compounds of Formula Iaa, R^{173} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{173} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{173} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0187] In some embodiments of compounds of Formula Iaa, further to any of the above embodiments of Formula Iaa, R^{174} is cycloalkyl or lower alkyl.

[0188] In some embodiments of compounds of Formula Iaa, further to any of the above embodiments of Formula Iaa, R^{174} is C_{3-6} cycloalkyl or lower alkyl.

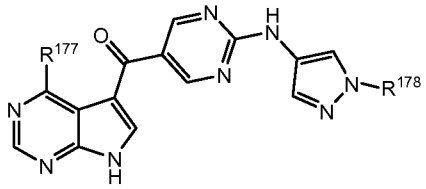
[0189] In some embodiments of compounds of Formula Iaa, further to any of the above embodiments of Formula Iaa, R^{174} is cyclopropyl or lower alkyl.

[0190] In some embodiments of compounds of Formula Iaa, further to any of the above embodiments of Formula Iaa, R^{174} is lower alkyl.

[0191] In some embodiments of compounds of Formula Iaa, further to any of the above embodiments of Formula Iaa, R^{174} is C_{1-3} alkyl.

[0192] In some embodiments of compounds of Formula Iaa, further to any of the above embodiments of Formula Iaa, R^{174} is ethyl.

[0193] In a twenty-eighth aspect, compounds of Formula I having the structure according to the following Formula Ibb are provided:



Formula Ibb

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{177} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{179}, and -O-R^{180};

R^{178} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro;

R^{179} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{180} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0194] In some embodiments of compounds of Formula Ibb, R^{177} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{177} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{177} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0195] In some embodiments of compounds of Formula Ibb, further to any of the above embodiments of Formula Ibb, R^{178} is cycloalkyl or lower alkyl.

[0196] In some embodiments of compounds of Formula Ibb, further to any of the above embodiments of Formula Ibb, R^{178} is C_{3-6} cycloalkyl or lower alkyl.

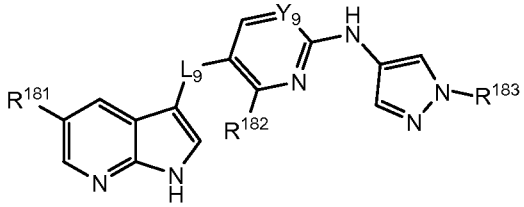
[0197] In some embodiments of compounds of Formula Ibb, further to any of the above embodiments of Formula Ibb, R^{178} is cyclopropyl or lower alkyl.

[0198] In some embodiments of compounds of Formula Ibb, further to any of the above embodiments of Formula Ibb, R^{178} is lower alkyl.

[0199] In some embodiments of compounds of Formula Ibb, further to any of the above embodiments of Formula Ibb, R^{178} is C_{1-3} alkyl.

[0200] In some embodiments of compounds of Formula Ibb, further to any of the above embodiments of Formula Ibb, R^{178} is ethyl.

[0201] In a twenty-ninth aspect, compounds of Formula I having the structure according to the following Formula Icc are provided:



Formula Icc

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Y_9 is –N= and R^{182} is hydrogen; or Y_9 is-C(H)= and R^{182} is fluoro;

L_9 is -$C(H_2)$- or -C(O)-;

R^{181} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro; and

R^{183} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro.

[0202] In some embodiments of compounds of Formula Icc, R^{181} is hydrogen, chloro or lower alkyl. In one embodiment, R^{181} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{181} is hydrogen, chloro or methyl.

[0203] In some embodiments of compounds of Formula Icc, further to any of the above embodiments of Formula Icc, R^{183} is cycloalkyl or lower alkyl.

[0204] In some embodiments of compounds of Formula Icc, further to any of the above embodiments of Formula Icc, R^{183} is C_{3-6} cycloalkyl or lower alkyl.

[0205] In some embodiments of compounds of Formula Icc, further to any of the above embodiments of Formula Icc, R^{183} is cyclopropyl or lower alkyl.

[0206] In some embodiments of compounds of Formula Icc, further to any of the above embodiments of Formula Icc, R^{183} is lower alkyl.

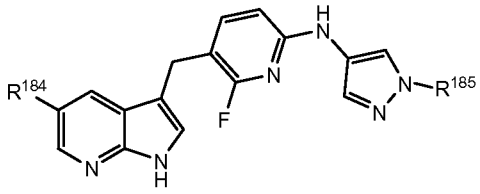
[0207] In some embodiments of compounds of Formula Icc, further to any of the above embodiments of Formula Icc, R^{183} is C_{1-3} alkyl.

[0208] In some embodiments of compounds of Formula Icc, further to any of the above embodiments of Formula Icc, R^{183} is ethyl.

[0209] In some embodiments of compounds of Formula Icc, further to any of the above embodiments of Formula Icc, L_9 is $-C(H_2)-$. In some embodiments of compounds of Formula Icc, further to any of the above embodiments of Formula Icc, L_9 is -C(O)-.

[0210] In some embodiments of compounds of Formula Icc, further to any of the above embodiments of Formula Icc, Y_9 is –N= and R^{182} is hydrogen. In some embodiments of compounds of Formula Icc, further to any of the above embodiments of Formula Icc, Y_9 is -C(H)= and R^{182} is fluoro.

[0211] In a thirtieth aspect, compounds of Formula I having the structure according to the following Formula Idd are provided:



Formula Idd

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{184} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro; and

R^{185} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro.

[0212] In some embodiments of compounds of Formula Idd, R^{184} is hydrogen, chloro or lower alkyl. In one embodiment, R^{184} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{184} is hydrogen, chloro or methyl.

[0213] In some embodiments of compounds of Formula Idd, further to any of the above embodiments of Formula Idd, R^{185} is cycloalkyl or lower alkyl.

[0214] In some embodiments of compounds of Formula Idd, further to any of the above embodiments of Formula Idd, R^{185} is C_{3-6} cycloalkyl or lower alkyl.

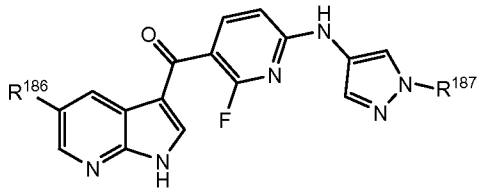
[0215] In some embodiments of compounds of Formula Idd, further to any of the above embodiments of Formula Idd, R^{185} is cyclopropyl or lower alkyl.

[0216] In some embodiments of compounds of Formula Idd, further to any of the above embodiments of Formula Idd, R^{185} is lower alkyl.

[0217] In some embodiments of compounds of Formula Idd, further to any of the above embodiments of Formula Idd, R^{185} is C_{1-3} alkyl.

[0218] In some embodiments of compounds of Formula Idd, further to any of the above embodiments of Formula Idd, R^{185} is ethyl.

[0219] In a thirty-first aspect, compounds of Formula I having the structure according to the following Formula Iee are provided:



Formula Iee

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{186} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro; and

R^{187} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro.

[0220] In some embodiments of compounds of Formula Iee, R^{186} is hydrogen, chloro or lower alkyl. In one embodiment, R^{186} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{186} is hydrogen, chloro or methyl.

[0221] In some embodiments of compounds of Formula Iee, further to any of the above embodiments of Formula Iee, R^{187} is cycloalkyl or lower alkyl.

[0222] In some embodiments of compounds of Formula Iee, further to any of the above embodiments of Formula Iee, R^{187} is C_{3-6} cycloalkyl or lower alkyl.

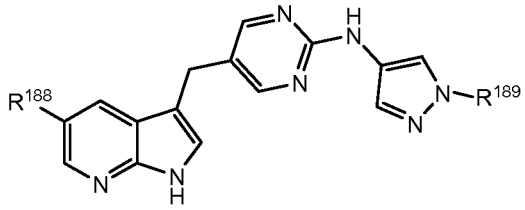
[0223] In some embodiments of compounds of Formula Iee, further to any of the above embodiments of Formula Iee, R^{187} is cyclopropyl or lower alkyl.

[0224] In some embodiments of compounds of Formula Iee, further to any of the above embodiments of Formula Iee, R^{187} is lower alkyl.

[0225] In some embodiments of compounds of Formula Iee, further to any of the above embodiments of Formula Iee, R^{187} is C_{1-3} alkyl.

[0226] In some embodiments of compounds of Formula Iee, further to any of the above embodiments of Formula Iee, R^{187} is ethyl.

[0227] In a thirty-second aspect, compounds of Formula I having the structure according to the following Formula Iff are provided:



Formula Iff

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{188} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro; and

R^{189} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro.

[0228] In some embodiments of compounds of Formula Iff, R^{188} is hydrogen, chloro or lower alkyl. In one embodiment, R^{188} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{188} is hydrogen, chloro or methyl.

[0229] In some embodiments of compounds of Formula Iff, further to any of the above embodiments of Formula Iff, R^{189} is cycloalkyl or lower alkyl.

[0230] In some embodiments of compounds of Formula Iff, further to any of the above embodiments of Formula Iff, R^{189} is C_{3-6} cycloalkyl or lower alkyl.

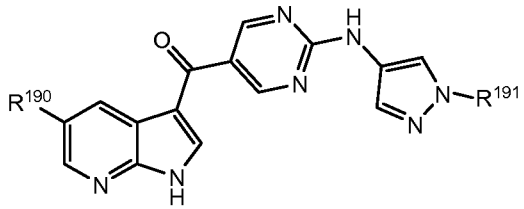
[0231] In some embodiments of compounds of Formula Iff, further to any of the above embodiments of Formula Iff, R^{189} is cyclopropyl or lower alkyl.

[0232] In some embodiments of compounds of Formula Iff, further to any of the above embodiments of Formula Iff, R^{189} is lower alkyl.

[0233] In some embodiments of compounds of Formula Iff, further to any of the above embodiments of Formula Iff, R^{189} is C_{1-3} alkyl.

[0234] In some embodiments of compounds of Formula Iff, further to any of the above embodiments of Formula Iff, R^{189} is ethyl.

[0235] In a thirty-third aspect, compounds of Formula I having the structure according to the following Formula Igg are provided:



Formula Igg

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{190} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro; and

R^{191} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro.

[0236] In some embodiments of compounds of Formula Igg, R^{190} is hydrogen, chloro or lower alkyl. In one embodiment, R^{190} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{190} is hydrogen, chloro or methyl.

[0237] In some embodiments of compounds of Formula Igg, further to any of the above embodiments of Formula Igg, R^{191} is cycloalkyl or lower alkyl.

[0238] In some embodiments of compounds of Formula Igg, further to any of the above embodiments of Formula Igg, R^{191} is C_{3-6} cycloalkyl or lower alkyl.

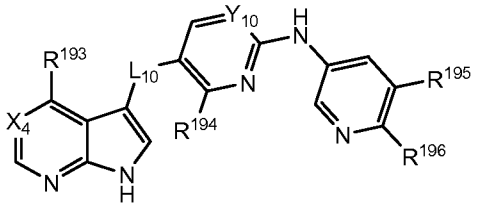
[0239] In some embodiments of compounds of Formula Igg, further to any of the above embodiments of Formula Igg, R^{191} is cyclopropyl or lower alkyl.

[0240] In some embodiments of compounds of Formula Igg, further to any of the above embodiments of Formula Igg, R^{191} is lower alkyl.

[0241] In some embodiments of compounds of Formula Igg, further to any of the above embodiments of Formula Igg, R^{191} is C_{1-3} alkyl.

[0242] In some embodiments of compounds of Formula Igg, further to any of the above embodiments of Formula Igg, R^{191} is ethyl.

[0243] In a thirty-fourth aspect, compounds of Formula I having the structure according to the following Formula Ihh are provided:



Formula Ihh

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

X_4 is –N=, -C(H)=, or -C(R^{192})= ;

Y_{10} is –N= and R^{194} is hydrogen; or Y_{10} is-C(H)= and R^{194} is fluoro;

L_{10} is -C(H_2)- or -C(O)-;

when X_4 is -C(R^{192})=, R^{193} is hydrogen;

when X_4 is –N= or -C(H)=, R^{193} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{197}, and -O-R^{198};

R^{192} is fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

R^{195} is hydrogen and R^{196} is hydrogen, fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro; or

R^{196} is hydrogen and R^{195} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro;

R^{197} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{198} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0244] In some embodiments of compounds of Formula Ihh, X_4 is –N= and R^{193} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{197}, and -O-R^{198}. In one embodiment, X_4 is –N= and R^{193} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, X_4 is –N= and R^{193} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, X_4 is -N= and R^{193} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0245] In some embodiments of compounds of Formula Ihh, X_4 is -C(H)= or -C(R^{192})= and R^{192} is fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro. In one embodiment, X_4 is -C(H)= or -C(R^{192})= and R^{192} is chloro or lower alkyl. In one embodiment, X_4 is -C(H)= or -C(R^{192})= and R^{192} is chloro or C_{1-3} alkyl. In one embodiment, X_4 is -C(H)= or -C(R^{192})= and R^{192} is chloro or methyl.

[0246] In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{196} is hydrogen and R^{195} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{196} is hydrogen and R^{195} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{196} is hydrogen and R^{195} is lower alkyl. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{196} is hydrogen and R^{195} is C_{1-3} alkyl. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{196} is hydrogen and R^{195} is methyl.

[0247] In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is fluoro, chloro, bromo. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

[0248] In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is cycloalkyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is cyclopropyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is cyclopropyl, trifluoromethyl, methyl or ethyl.

[0249] In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is cycloalkyl. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is cyclopropyl.

[0250] In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ihh, further to any of the above

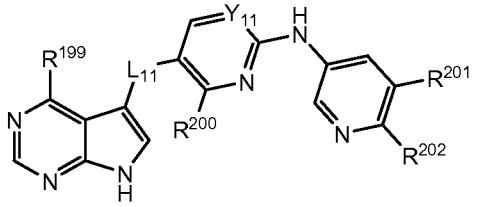
embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is trifluoromethyl, methyl or ethyl. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is trifluoromethyl. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is methyl. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is ethyl.

[0251] In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is lower alkoxy. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is C_{1-3} alkoxy. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is methoxy or ethoxy. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is methoxy. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, R^{195} is hydrogen and R^{196} is ethoxy.

[0252] In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, L_{10} is $-C(H_2)-$. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, L_{10} is -C(O)-.

[0253] In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, Y_{10} is –N= and R^{194} is hydrogen. In some embodiments of compounds of Formula Ihh, further to any of the above embodiments of Formula Ihh, Y_{10} is -C(H)= and R^{194} is fluoro.

[0254] In a thirty-fifth aspect, compounds of Formula I having the structure according to the following Formula Iii are provided:



Formula Iii

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Y_{11} is –N= and R^{200} is hydrogen; or Y_{11} is-C(H)= and R^{200} is fluoro;

L_{11} is -$C(H_2)$- or -C(O)-;

R^{199} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{203}, and -O-R^{204};

R^{201} is hydrogen and R^{202} is hydrogen, fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro; or

R^{202} is hydrogen and R^{201} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro;

R^{203} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{204} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0255] In some embodiments of compounds of Formula Iii, R^{199} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{199} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{199} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0256] In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{202} is hydrogen and R^{201} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{202} is hydrogen and R^{201} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{202} is hydrogen and R^{201} is lower alkyl. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{202} is hydrogen and R^{201} is C_{1-3} alkyl. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{202} is hydrogen and R^{201} is methyl.

[0257] In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is fluoro, chloro, bromo. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

[0258] In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is cycloalkyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is cyclopropyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is cyclopropyl, trifluoromethyl, methyl or ethyl.

[0259] In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is cycloalkyl. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is cyclopropyl.

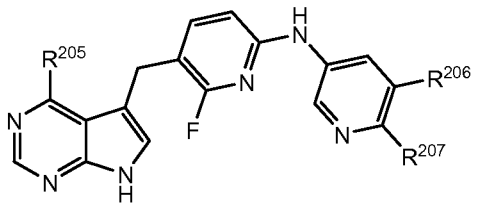
[0260] In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is trifluoromethyl, methyl or ethyl. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is trifluoromethyl. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is methyl. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is ethyl.

[0261] In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is lower alkoxy. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is C_{1-3} alkoxy. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is methoxy or ethoxy. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is methoxy. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, R^{201} is hydrogen and R^{202} is ethoxy.

[0262] In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, L_{11} is -C(H_2)-. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, L_{11} is -C(O)-.

[0263] In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, Y_{11} is –N= and R^{200} is hydrogen. In some embodiments of compounds of Formula Iii, further to any of the above embodiments of Formula Iii, Y_{11} is-C(H)= and R^{200} is fluoro.

[0264] In a thirty-sixth aspect, compounds of Formula I having the structure according to the following Formula Ijj are provided:



Formula Ijj

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{205} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{208}, and -O-R^{209};

R^{206} is hydrogen and R^{207} is hydrogen, fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro; or

R^{207} is hydrogen and R^{206} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro;

R^{208} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{209} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0265] In some embodiments of compounds of Formula Ijj, R^{205} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{205} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{205} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0266] In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{207} is hydrogen and R^{206} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one

or more fluoro. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{207} is hydrogen and R^{206} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{207} is hydrogen and R^{206} is lower alkyl. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{207} is hydrogen and R^{206} is C_{1-3} alkyl. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{207} is hydrogen and R^{206} is methyl.

[0267] In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is fluoro, chloro, bromo. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

[0268] In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is cycloalkyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is cyclopropyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is cyclopropyl, trifluoromethyl, methyl or ethyl.

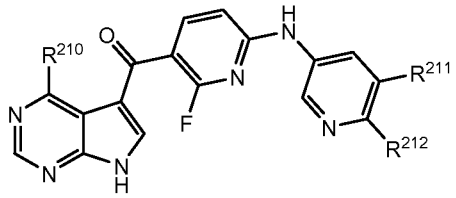
[0269] In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is cycloalkyl. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is cyclopropyl.

[0270] In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is trifluoromethyl, methyl or ethyl. In some

embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is trifluoromethyl. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is methyl. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is ethyl.

[0271] In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is lower alkoxy. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is C_{1-3} alkoxy. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is methoxy or ethoxy. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is methoxy. In some embodiments of compounds of Formula Ijj, further to any of the above embodiments of Formula Ijj, R^{206} is hydrogen and R^{207} is ethoxy.

[0272] In a thirty-seventh aspect, compounds of Formula I having the structure according to the following Formula Ikk are provided:



Formula Ikk

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{210} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{213}, and -O-R^{214};

R^{211} is hydrogen and R^{212} is hydrogen, fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro; or

R^{212} is hydrogen and R^{211} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro;

R^{213} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{214} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0273] In some embodiments of compounds of Formula Ikk, R^{210} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{210} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{210} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0274] In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{212} is hydrogen and R^{211} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{212} is hydrogen and R^{211} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{212} is hydrogen and R^{211} is lower alkyl. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{212} is hydrogen and R^{211} is C_{1-3} alkyl. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{212} is hydrogen and R^{211} is methyl.

[0275] In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is fluoro, chloro, bromo. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

[0276] In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is cycloalkyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is cyclopropyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is cyclopropyl, trifluoromethyl, methyl or ethyl.

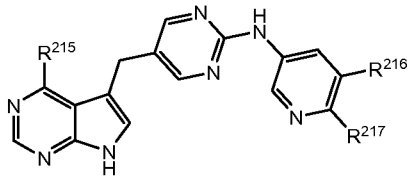
[0277] In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is cycloalkyl. In some embodiments of

compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is cyclopropyl.

[0278] In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is trifluoromethyl, methyl or ethyl. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is trifluoromethyl. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is methyl. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is ethyl.

[0279] In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is lower alkoxy. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is C_{1-3} alkoxy. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is methoxy or ethoxy. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is methoxy. In some embodiments of compounds of Formula Ikk, further to any of the above embodiments of Formula Ikk, R^{211} is hydrogen and R^{212} is ethoxy.

[0280] In a thirty-eighth aspect, compounds of Formula I having the structure according to the following Formula Imm are provided:



Formula Imm

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{215} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{218}, and -O-R^{219};

R^{216} is hydrogen and R^{217} is hydrogen, fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro; or

R^{217} is hydrogen and R^{216} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro;

R^{218} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{219} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0281] In some embodiments of compounds of Formula Imm, R^{215} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{215} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{215} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0282] In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{217} is hydrogen and R^{216} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{217} is hydrogen and R^{216} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{217} is hydrogen and R^{216} is lower alkyl. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{217} is hydrogen and R^{216} is C_{1-3} alkyl. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{217} is hydrogen and R^{216} is methyl.

[0283] In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is fluoro, chloro, bromo. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

[0284] In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Imm, further to

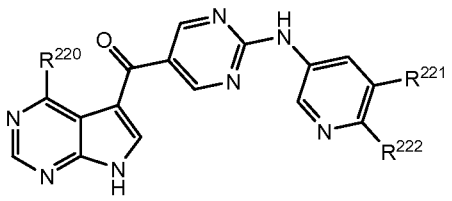
any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is cycloalkyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is cyclopropyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is cyclopropyl, trifluoromethyl, methyl or ethyl.

[0285] In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is cycloalkyl. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is cyclopropyl.

[0286] In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is trifluoromethyl, methyl or ethyl. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is trifluoromethyl. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is methyl. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is ethyl.

[0287] In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is lower alkoxy. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is C_{1-3} alkoxy. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is methoxy or ethoxy. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is methoxy. In some embodiments of compounds of Formula Imm, further to any of the above embodiments of Formula Imm, R^{216} is hydrogen and R^{217} is ethoxy.

[0288] In a thirty-ninth aspect, compounds of Formula I having the structure according to the following Formula Inn are provided:



Formula Inn

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{220} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{223}, and -O-R^{224};

R^{221} is hydrogen and R^{222} is hydrogen, fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro; or

R^{222} is hydrogen and R^{221} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro;

R^{223} is fluoro or lower alkoxy optionally substitituted with one or more fluoro; and

R^{224} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy.

[0289] In some embodiments of compounds of Formula Inn, R^{220} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{220} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{220} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0290] In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{222} is hydrogen and R^{221} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{222} is hydrogen and R^{221} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{222} is hydrogen and R^{221} is lower alkyl. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{222} is hydrogen and R^{221} is C_{1-3} alkyl. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{222} is hydrogen and R^{221} is methyl.

[0291] In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is fluoro, chloro, bromo, cycloalkyl, lower

alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is fluoro, chloro, bromo. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

[0292] In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is cycloalkyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is cyclopropyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is cyclopropyl, trifluoromethyl, methyl or ethyl.

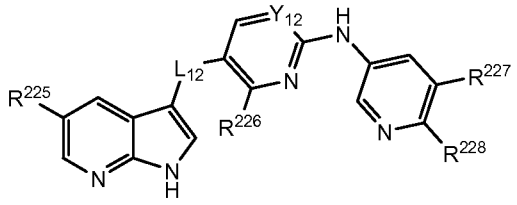
[0293] In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is cycloalkyl. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is cyclopropyl.

[0294] In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is trifluoromethyl, methyl or ethyl. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is trifluoromethyl. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is methyl. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is ethyl.

[0295] In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is lower alkoxy. In some embodiments of

compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is C_{1-3} alkoxy. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is methoxy or ethoxy. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is methoxy. In some embodiments of compounds of Formula Inn, further to any of the above embodiments of Formula Inn, R^{221} is hydrogen and R^{222} is ethoxy.

[0296] In a fortieth aspect, compounds of Formula I having the structure according to the following Formula Ioo are provided:



Formula Ioo

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Y_{12} is –N= and R^{226} is hydrogen; or Y_{12} is-C(H)= and R^{226} is fluoro;

L_{12} is -$C(H_2)$- or -C(O)-;

R^{225} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

R^{227} is hydrogen and R^{228} is hydrogen, fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro; or

R^{228} is hydrogen and R^{227} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

[0297] In some embodiments of compounds of Formula Ioo, R^{225} is hydrogen, chloro or lower alkyl. In one embodiment, R^{225} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{225} is hydrogen, chloro or methyl.

[0298] In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{228} is hydrogen and R^{227} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{228} is hydrogen and R^{227} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{228} is hydrogen and R^{227} is lower alkyl. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{228} is

hydrogen and R^{227} is C_{1-3} alkyl. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{228} is hydrogen and R^{227} is methyl.

[0299] In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is fluoro, chloro, bromo. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

[0300] In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is cycloalkyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is cyclopropyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is cyclopropyl, trifluoromethyl, methyl or ethyl.

[0301] In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is cycloalkyl. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is cyclopropyl.

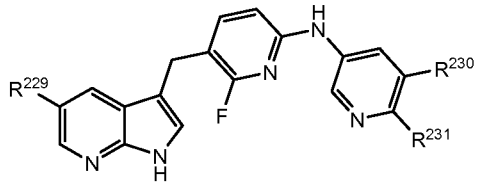
[0302] In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is trifluoromethyl, methyl or ethyl. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is trifluoromethyl. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is methyl. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is ethyl.

[0303] In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is lower alkoxy. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is C_{1-3} alkoxy. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is methoxy or ethoxy. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is methoxy. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, R^{227} is hydrogen and R^{228} is ethoxy.

[0304] In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, L_{12} is $-C(H_2)-$. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, L_{12} is -C(O)-.

[0305] In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, Y_{12} is –N= and R^{226} is hydrogen. In some embodiments of compounds of Formula Ioo, further to any of the above embodiments of Formula Ioo, Y_{12} is -C(H)= and R^{226} is fluoro.

[0306] In a forty-first aspect, compounds of Formula I having the structure according to the following Formula Ipp are provided:



Formula Ipp

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{229} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

R^{230} is hydrogen and R^{231} is hydrogen, fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro; or

R^{231} is hydrogen and R^{230} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

[0307] In some embodiments of compounds of Formula Ipp, R^{229} is hydrogen, chloro or lower alkyl. In one embodiment, R^{229} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{229} is hydrogen, chloro or methyl.

[0308] In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{231} is hydrogen and R^{230} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{231} is hydrogen and R^{230} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{231} is hydrogen and R^{230} is lower alkyl. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{231} is hydrogen and R^{230} is C_{1-3} alkyl. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{231} is hydrogen and R^{230} is methyl.

[0309] In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is fluoro, chloro, bromo. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

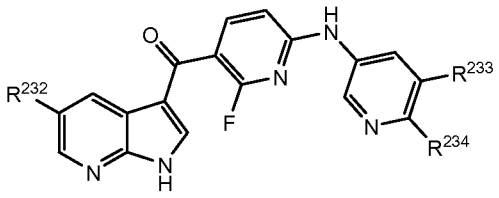
[0310] In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is cycloalkyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is cyclopropyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is cyclopropyl, trifluoromethyl, methyl or ethyl.

[0311] In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is cycloalkyl. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is cyclopropyl.

[0312] In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is trifluoromethyl, methyl or ethyl. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is trifluoromethyl. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is methyl. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is ethyl.

[0313] In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is lower alkoxy. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is C_{1-3} alkoxy. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is methoxy or ethoxy. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is methoxy. In some embodiments of compounds of Formula Ipp, further to any of the above embodiments of Formula Ipp, R^{230} is hydrogen and R^{231} is ethoxy.

[0314] In a forty-second aspect, compounds of Formula I having the structure according to the following Formula Iqq are provided:



Formula Iqq

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{232} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

R^{233} is hydrogen and R^{234} is hydrogen, fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro; or

R^{234} is hydrogen and R^{233} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

[0315] In some embodiments of compounds of Formula Iqq, R^{232} is hydrogen, chloro or lower alkyl. In one embodiment, R^{232} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{232} is hydrogen, chloro or methyl.

[0316] In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{234} is hydrogen and R^{233} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{234} is hydrogen and R^{233} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{234} is hydrogen and R^{233} is lower alkyl. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{234} is hydrogen and R^{233} is C_{1-3} alkyl. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{234} is hydrogen and R^{233} is methyl.

[0317] In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is fluoro, chloro, bromo. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

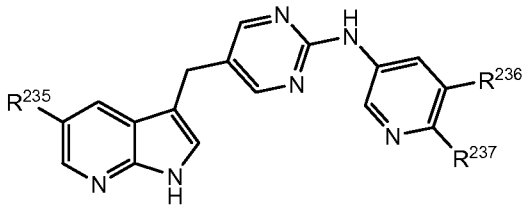
[0318] In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is cycloalkyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is cyclopropyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is cyclopropyl, trifluoromethyl, methyl or ethyl.

[0319] In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is cycloalkyl. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is cyclopropyl.

[0320] In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is trifluoromethyl, methyl or ethyl. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is trifluoromethyl. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is methyl. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is ethyl.

[0321] In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is lower alkoxy. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is C_{1-3} alkoxy. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is methoxy or ethoxy. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is methoxy. In some embodiments of compounds of Formula Iqq, further to any of the above embodiments of Formula Iqq, R^{233} is hydrogen and R^{234} is ethoxy.

[0322] In a forty-third aspect, compounds of Formula I having the structure according to the following Formula Irr are provided:



Formula Irr

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{235} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

R^{236} is hydrogen and R^{237} is hydrogen, fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro; or

R^{237} is hydrogen and R^{236} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

[0323] In some embodiments of compounds of Formula Irr, R^{235} is hydrogen, chloro or lower alkyl. In one embodiment, R^{235} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{235} is hydrogen, chloro or methyl.

[0324] In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{237} is hydrogen and R^{236} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{237} is hydrogen and R^{236} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{237} is hydrogen and R^{236} is lower alkyl. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{237} is hydrogen and R^{236} is C_{1-3} alkyl. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{237} is hydrogen and R^{236} is methyl.

[0325] In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is fluoro, chloro, bromo. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

[0326] In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is cycloalkyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is cyclopropyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of

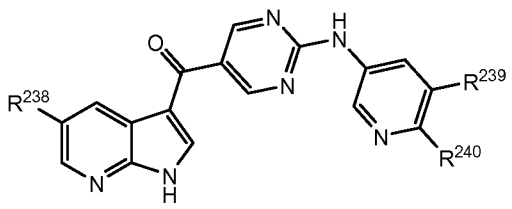
Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is cyclopropyl, trifluoromethyl, methyl or ethyl.

[0327] In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is cycloalkyl. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is cyclopropyl.

[0328] In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is trifluoromethyl, methyl or ethyl. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is trifluoromethyl. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is methyl. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is ethyl.

[0329] In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is lower alkoxy. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is C_{1-3} alkoxy. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is methoxy or ethoxy. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is methoxy. In some embodiments of compounds of Formula Irr, further to any of the above embodiments of Formula Irr, R^{236} is hydrogen and R^{237} is ethoxy.

[0330] In a forty-fourth aspect, compounds of Formula I having the structure according to the following Formula Iss are provided:



Formula Iss

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{238} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

R^{239} is hydrogen and R^{240} is hydrogen, fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro; or

R^{240} is hydrogen and R^{239} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

[0331] In some embodiments of compounds of Formula Iss, R^{238} is hydrogen, chloro or lower alkyl. In one embodiment, R^{238} is hydrogen, chloro or C_{1-3} alkyl. In one embodiment, R^{238} is hydrogen, chloro or methyl.

[0332] In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{240} is hydrogen and R^{239} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{240} is hydrogen and R^{239} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{240} is hydrogen and R^{239} is lower alkyl. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{240} is hydrogen and R^{239} is C_{1-3} alkyl. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{240} is hydrogen and R^{239} is methyl.

[0333] In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is fluoro, chloro, bromo. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is cycloalkyl, lower alkyl optionally substituted with one or more fluoro, or lower alkoxy optionally substituted with one or more fluoro.

[0334] In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is cycloalkyl or lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is cycloalkyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Iss,

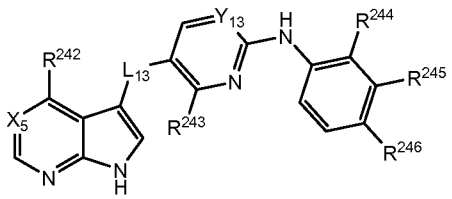
further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is cyclopropyl or C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is cyclopropyl, trifluoromethyl, methyl or ethyl.

[0335] In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is cycloalkyl. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is cyclopropyl.

[0336] In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is lower alkyl optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is C_{1-3} alkyl optionally substituted with 1, 2, or 3 fluoro. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is trifluoromethyl, methyl or ethyl. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is trifluoromethyl. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is methyl. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is ethyl.

[0337] In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is lower alkoxy optionally substituted with one or more fluoro. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is lower alkoxy. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is C_{1-3} alkoxy. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is methoxy or ethoxy. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is methoxy. In some embodiments of compounds of Formula Iss, further to any of the above embodiments of Formula Iss, R^{239} is hydrogen and R^{240} is ethoxy.

[0338] In a forty-fifth aspect, compounds of Formula I having the structure according to the following Formula Itt are provided:



Formula Itt

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

X_5 is –N=, -C(H)=, or -C(R^{241})= ;

Y_{13} is –N= and R^{243} is hydrogen; or Y_{13} is-C(H)= and R^{243} is fluoro;

L_{13} is -C(H_2)- or -C(O)-;

when X_5 is -C(R^{241})=, R^{242} is hydrogen;

when X_5 is –N= or -C(H)=, R^{242} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{247}, and -O-R^{248};

R^{241} is fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

R^{244} and R^{245} are hydrogen and R^{246} is selected from the group consisting of fluoro, chloro, -O-R^{249}, -S-R^{250}, -S(O_2)-R^{251}, and lower alkyl optionally substitituted with one or more R^{252}; or

R^{244} and R^{246} are hydrogen and R^{245} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{245} and R^{246} are hydrogen and R^{244} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{244} is hydrogen, R^{245} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{246} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro;

R^{247} is fluoro or lower alkoxy optionally substitituted with one or more fluoro;

R^{248} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy;

R^{249}, R^{250} and R^{251} are lower alkyl optionally substituted with one or more fluoro; and

R^{252} is fluoro, -OH, or lower alkoxy optionally substituted with one or more fluoro.

[0339] In some embodiments of compounds of Formula Itt, X_5 is –N= and R^{242} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{247}, and -O-R^{248}. In one embodiment, X_5 is –N= and R^{242} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, X_5 is –N= and R^{242} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl,

C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, X_5 is -N= and R^{242} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0340] In some embodiments of compounds of Formula Itt, X_5 is -C(H)= or -C(R^{241})= and R^{241} is fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro. In one embodiment, X_5 is -C(H)= or -C(R^{241})= and R^{241} is chloro or lower alkyl. In one embodiment, X_5 is -C(H)= or -C(R^{241})= and R^{241} is chloro or C_{1-3} alkyl. In one embodiment, X_5 is -C(H)= or -C(R^{241})= and R^{241} is chloro or methyl.

[0341] In some embodiments of compounds of Formula Itt, further to any of the above embodiments of Formula Itt, R^{244} and R^{245} are hydrogen and R^{246} is selected from the group consisting of fluoro, chloro, -O-R^{249}, -S-R^{250}, -S(O_2)-R^{251}, and lower alkyl optionally substitituted with one or more R^{252}. In some embodiments of compounds of Formula Itt, further to any of the above embodiments of Formula Itt, R^{244} and R^{245} are hydrogen and R^{246} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl optionally substitituted with one or more fluoro or -OH. In some embodiments of compounds of Formula Itt, further to any of the above embodiments of Formula Itt, R^{244} and R^{245} are hydrogen and R^{246} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl.

[0342] In some embodiments of compounds of Formula Itt, further to any of the above embodiments of Formula Itt, R^{244} and R^{246} are hydrogen and R^{245} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Itt, further to any of the above embodiments of Formula Itt, R^{244} and R^{246} are hydrogen and R^{245} is fluoro, chloro, lower alkyl or lower alkoxy.

[0343] In some embodiments of compounds of Formula Itt, further to any of the above embodiments of Formula Itt, R^{245} and R^{246} are hydrogen and R^{244} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Itt, further to any of the above embodiments of Formula Itt, R^{245} and R^{246} are hydrogen and R^{244} is fluoro, chloro, lower alkyl or lower alkoxy.

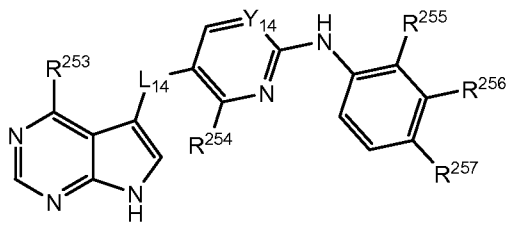
[0344] In some embodiments of compounds of Formula Itt, further to any of the above embodiments of Formula Itt, R^{244} is hydrogen, R^{245} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{246} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower

alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Itt, further to any of the above embodiments of Formula Itt, R^{244} is hydrogen, R^{245} is fluoro, chloro, lower alkyl or lower alkoxy and R^{246} is fluoro, chloro, lower alkyl or lower alkoxy. In some embodiments of compounds of Formula Itt, further to any of the above embodiments of Formula Itt, R^{244} is hydrogen, R^{245} is fluoro, chloro, or lower alkoxy and R^{246} is fluoro, chloro, or lower alkoxy.

[0345] In some embodiments of compounds of Formula Itt, further to any of the above embodiments of Formula Itt, L_{13} is $-C(H_2)-$. In some embodiments of compounds of Formula Itt, further to any of the above embodiments of Formula Itt, L_{13} is -C(O)-.

[0346] In some embodiments of compounds of Formula Itt, further to any of the above embodiments of Formula Itt, Y_{13} is –N= and R^{243} is hydrogen. In some embodiments of compounds of Formula Itt, further to any of the above embodiments of Formula Itt, Y_{13} is -C(H)= and R^{243} is fluoro.

[0347] In a forty-sixth aspect, compounds of Formula I having the structure according to the following Formula Iuu are provided:



Formula Iuu

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Y_{14} is –N= and R^{254} is hydrogen; or Y_{14} is-C(H)= and R^{254} is fluoro;

L_{14} is $-C(H_2)-$ or -C(O)-;

R^{253} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{258}, and $-O-R^{259}$;

R^{255} and R^{256} are hydrogen and R^{257} is selected from the group consisting of fluoro, chloro, $-O-R^{260}$, $-S-R^{261}$, $-S(O_2)-R^{262}$, and lower alkyl optionally substitituted with one or more R^{263}; or

R^{255} and R^{257} are hydrogen and R^{256} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{256} and R^{257} are hydrogen and R^{255} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{255} is hydrogen, R^{256} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{257} is fluoro,

chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro;

R^{258} is fluoro or lower alkoxy optionally substitituted with one or more fluoro;

R^{259} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy;

R^{260}, R^{261} and R^{262} are lower alkyl optionally substituted with one or more fluoro; and

R^{263} is fluoro, -OH, or lower alkoxy optionally substituted with one or more fluoro.

[0348] In some embodiments of compounds of Formula Iuu, R^{253} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{253} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{253} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0349] In some embodiments of compounds of Formula Iuu, further to any of the above embodiments of Formula Iuu, R^{255} and R^{256} are hydrogen and R^{257} is selected from the group consisting of fluoro, chloro, -O-R^{260}, -S-R^{261}, -S(O_2)-R^{262}, and lower alkyl optionally substitituted with one or more R^{263}. In some embodiments of compounds of Formula Iuu, further to any of the above embodiments of Formula Iuu, R^{255} and R^{256} are hydrogen and R^{257} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl optionally substitituted with one or more fluoro or -OH. In some embodiments of compounds of Formula Iuu, further to any of the above embodiments of Formula Iuu, R^{255} and R^{256} are hydrogen and R^{257} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl.

[0350] In some embodiments of compounds of Formula Iuu, further to any of the above embodiments of Formula Iuu, R^{255} and R^{257} are hydrogen and R^{256} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iuu, further to any of the above embodiments of Formula Iuu, R^{255} and R^{257} are hydrogen and R^{256} is fluoro, chloro, lower alkyl or lower alkoxy.

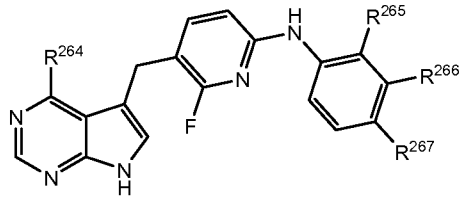
[0351] In some embodiments of compounds of Formula Iuu, further to any of the above embodiments of Formula Iuu, R^{256} and R^{257} are hydrogen and R^{255} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iuu, further to any of the above embodiments of Formula Iuu, R^{256} and R^{257} are hydrogen and R^{255} is fluoro, chloro, lower alkyl or lower alkoxy.

[0352] In some embodiments of compounds of Formula Iuu, further to any of the above embodiments of Formula Iuu, R^{255} is hydrogen, R^{256} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{257} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iuu, further to any of the above embodiments of Formula Iuu, R^{255} is hydrogen, R^{256} is fluoro, chloro, lower alkyl or lower alkoxy and R^{257} is fluoro, chloro, lower alkyl or lower alkoxy. In some embodiments of compounds of Formula Iuu, further to any of the above embodiments of Formula Iuu, R^{255} is hydrogen, R^{256} is fluoro, chloro, or lower alkoxy and R^{257} is fluoro, chloro, or lower alkoxy.

[0353] In some embodiments of compounds of Formula Iuu, further to any of the above embodiments of Formula Iuu, L_{14} is $-C(H_2)-$. In some embodiments of compounds of Formula Iuu, further to any of the above embodiments of Formula Iuu, L_{14} is -C(O)-.

[0354] In some embodiments of compounds of Formula Iuu, further to any of the above embodiments of Formula Iuu, Y_{14} is –N= and R^{254} is hydrogen. In some embodiments of compounds of Formula Iuu, further to any of the above embodiments of Formula Iuu, Y_{14} is -C(H)= and R^{254} is fluoro.

[0355] In a forty-seventh aspect, compounds of Formula I having the structure according to the following Formula Ivv are provided:



Formula Ivv

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{264} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{268}, and $-O-R^{269}$;

R^{265} and R^{266} are hydrogen and R^{267} is selected from the group consisting of fluoro, chloro, $-O-R^{270}$, $-S-R^{271}$, $-S(O_2)-R^{272}$, and lower alkyl optionally substitituted with one or more R^{273}; or

R^{265} and R^{267} are hydrogen and R^{266} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{266} and R^{267} are hydrogen and R^{265} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{265} is hydrogen, R^{266} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{267} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro;

R^{268} is fluoro or lower alkoxy optionally substitituted with one or more fluoro;

R^{269} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy;

R^{270}, R^{271} and R^{272} are lower alkyl optionally substituted with one or more fluoro; and

R^{273} is fluoro, -OH, or lower alkoxy optionally substituted with one or more fluoro.

[0356] In some embodiments of compounds of Formula Ivv, R^{264} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{264} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{264} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0357] In some embodiments of compounds of Formula Ivv, further to any of the above embodiments of Formula Ivv, R^{265} and R^{266} are hydrogen and R^{267} is selected from the group consisting of fluoro, chloro, -O-R^{270}, -S-R^{271}, -S(O_2)-R^{272}, and lower alkyl optionally substitituted with one or more R^{273}. In some embodiments of compounds of Formula Ivv, further to any of the above embodiments of Formula Ivv, R^{265} and R^{266} are hydrogen and R^{267} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl optionally substitituted with one or more fluoro or -OH. In some embodiments of compounds of Formula Ivv, further to any of the above embodiments of Formula Ivv, R^{265} and R^{266} are hydrogen and R^{267} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl.

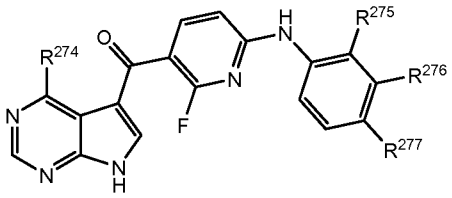
[0358] In some embodiments of compounds of Formula Ivv, further to any of the above embodiments of Formula Ivv, R^{265} and R^{267} are hydrogen and R^{266} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Ivv, further to any of the above embodiments of Formula Ivv, R^{265} and R^{267} are hydrogen and R^{266} is fluoro, chloro, lower alkyl or lower alkoxy.

[0359] In some embodiments of compounds of Formula Ivv, further to any of the above embodiments of Formula Ivv, R^{266} and R^{267} are hydrogen and R^{265} is fluoro, chloro, lower alkyl

optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Ivv, further to any of the above embodiments of Formula Ivv, R^{266} and R^{267} are hydrogen and R^{265} is fluoro, chloro, lower alkyl or lower alkoxy.

[0360] In some embodiments of compounds of Formula Ivv, further to any of the above embodiments of Formula Ivv, R^{265} is hydrogen, R^{266} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{267} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Ivv, further to any of the above embodiments of Formula Ivv, R^{265} is hydrogen, R^{266} is fluoro, chloro, lower alkyl or lower alkoxy and R^{267} is fluoro, chloro, lower alkyl or lower alkoxy. In some embodiments of compounds of Formula Ivv, further to any of the above embodiments of Formula Ivv, R^{265} is hydrogen, R^{266} is fluoro, chloro, or lower alkoxy and R^{267} is fluoro, chloro, or lower alkoxy.

[0361] In a forty-eighth aspect, compounds of Formula I having the structure according to the following Formula Iww are provided:



Formula Iww

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{274} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{278}, and -O-R^{279};

R^{275} and R^{276} are hydrogen and R^{277} is selected from the group consisting of fluoro, chloro, -O-R^{280}, -S-R^{281}, -S(O_2)-R^{282}, and lower alkyl optionally substitituted with one or more R^{283}; or

R^{275} and R^{277} are hydrogen and R^{276} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{276} and R^{277} are hydrogen and R^{275} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{275} is hydrogen, R^{276} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{277} is fluoro,

chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro;

R^{278} is fluoro or lower alkoxy optionally substitituted with one or more fluoro;

R^{279} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy;

R^{280}, R^{281} and R^{282} are lower alkyl optionally substituted with one or more fluoro; and

R^{283} is fluoro, -OH, or lower alkoxy optionally substituted with one or more fluoro.

[0362] In some embodiments of compounds of Formula Iww, R^{274} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{274} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{274} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

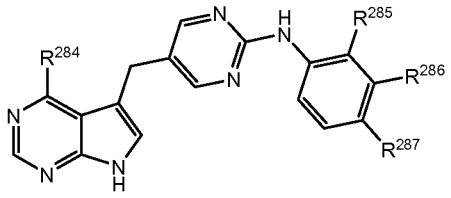
[0363] In some embodiments of compounds of Formula Iww, further to any of the above embodiments of Formula Iww, R^{275} and R^{276} are hydrogen and R^{277} is selected from the group consisting of fluoro, chloro, -O-R^{280}, -S-R^{281}, -S(O_2)-R^{282}, and lower alkyl optionally substitituted with one or more R^{283}. In some embodiments of compounds of Formula Iww, further to any of the above embodiments of Formula Iww, R^{275} and R^{276} are hydrogen and R^{277} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl optionally substitituted with one or more fluoro or -OH. In some embodiments of compounds of Formula Iww, further to any of the above embodiments of Formula Iww, R^{275} and R^{276} are hydrogen and R^{277} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl.

[0364] In some embodiments of compounds of Formula Iww, further to any of the above embodiments of Formula Iww, R^{275} and R^{277} are hydrogen and R^{276} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iww, further to any of the above embodiments of Formula Iww, R^{275} and R^{277} are hydrogen and R^{276} is fluoro, chloro, lower alkyl or lower alkoxy.

[0365] In some embodiments of compounds of Formula Iww, further to any of the above embodiments of Formula Iww, R^{276} and R^{277} are hydrogen and R^{275} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iww, further to any of the above embodiments of Formula Iww, R^{276} and R^{277} are hydrogen and R^{275} is fluoro, chloro, lower alkyl or lower alkoxy.

[0366] In some embodiments of compounds of Formula Iww, further to any of the above embodiments of Formula Iww, R^{275} is hydrogen, R^{276} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{277} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iww, further to any of the above embodiments of Formula Iww, R^{275} is hydrogen, R^{276} is fluoro, chloro, lower alkyl or lower alkoxy and R^{277} is fluoro, chloro, lower alkyl or lower alkoxy. In some embodiments of compounds of Formula Iww, further to any of the above embodiments of Formula Iww, R^{275} is hydrogen, R^{276} is fluoro, chloro, or lower alkoxy and R^{277} is fluoro, chloro, or lower alkoxy.

[0367] In a forty-ninth aspect, compounds of Formula I having the structure according to the following Formula Ixx are provided:



Formula Ixx

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{284} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{288}, and -O-R^{289};

R^{285} and R^{286} are hydrogen and R^{287} is selected from the group consisting of fluoro, chloro, -O-R^{290}, -S-R^{291}, -S(O_2)-R^{292}, and lower alkyl optionally substitituted with one or more R^{293}; or

R^{285} and R^{287} are hydrogen and R^{286} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{286} and R^{287} are hydrogen and R^{285} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{285} is hydrogen, R^{286} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{287} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro;

R^{288} is fluoro or lower alkoxy optionally substitituted with one or more fluoro;

R^{289} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy;

R^{290}, R^{291} and R^{292} are lower alkyl optionally substituted with one or more fluoro; and

R^{293} is fluoro, -OH, or lower alkoxy optionally substituted with one or more fluoro.

[0368] In some embodiments of compounds of Formula Ixx, R^{284} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{284} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{284} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

[0369] In some embodiments of compounds of Formula Ixx, further to any of the above embodiments of Formula Ixx, R^{285} and R^{286} are hydrogen and R^{287} is selected from the group consisting of fluoro, chloro, -O-R^{290}, -S-R^{291}, -S(O_2)-R^{292}, and lower alkyl optionally substitituted with one or more R^{293}. In some embodiments of compounds of Formula Ixx, further to any of the above embodiments of Formula Ixx, R^{285} and R^{286} are hydrogen and R^{287} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl optionally substitituted with one or more fluoro or -OH. In some embodiments of compounds of Formula Ixx, further to any of the above embodiments of Formula Ixx, R^{285} and R^{286} are hydrogen and R^{287} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl.

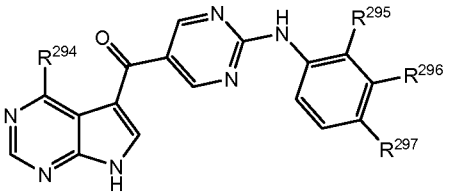
[0370] In some embodiments of compounds of Formula Ixx, further to any of the above embodiments of Formula Ixx, R^{285} and R^{287} are hydrogen and R^{286} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Ixx, further to any of the above embodiments of Formula Ixx, R^{285} and R^{287} are hydrogen and R^{286} is fluoro, chloro, lower alkyl or lower alkoxy.

[0371] In some embodiments of compounds of Formula Ixx, further to any of the above embodiments of Formula Ixx, R^{286} and R^{287} are hydrogen and R^{285} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Ixx, further to any of the above embodiments of Formula Ixx, R^{286} and R^{287} are hydrogen and R^{285} is fluoro, chloro, lower alkyl or lower alkoxy.

[0372] In some embodiments of compounds of Formula Ixx, further to any of the above embodiments of Formula Ixx, R^{285} is hydrogen, R^{286} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{287} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of

Formula Ixx, further to any of the above embodiments of Formula Ixx, R^{285} is hydrogen, R^{286} is fluoro, chloro, lower alkyl or lower alkoxy and R^{287} is fluoro, chloro, lower alkyl or lower alkoxy. In some embodiments of compounds of Formula Ixx, further to any of the above embodiments of Formula Ixx, R^{285} is hydrogen, R^{286} is fluoro, chloro, or lower alkoxy and R^{287} is fluoro, chloro, or lower alkoxy.

[0373] In a fiftieth aspect, compounds of Formula I having the structure according to the following Formula Iyy are provided:



Formula Iyy

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{294} is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^{298}, and -O-R^{299};

R^{295} and R^{296} are hydrogen and R^{297} is selected from the group consisting of fluoro, chloro, -O-R^{300}, -S-R^{301}, -S(O_2)-R^{302}, and lower alkyl optionally substitituted with one or more R^{303}; or

R^{295} and R^{297} are hydrogen and R^{296} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{296} and R^{297} are hydrogen and R^{295} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{295} is hydrogen, R^{296} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{297} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro;

R^{298} is fluoro or lower alkoxy optionally substitituted with one or more fluoro;

R^{299} is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy;

R^{300}, R^{301} and R^{302} are lower alkyl optionally substituted with one or more fluoro; and

R^{303} is fluoro, -OH, or lower alkoxy optionally substituted with one or more fluoro.

[0374] In some embodiments of compounds of Formula Iyy, R^{294} is selected from the group consisting of cycloalkyl, lower alkyl, lower alkoxy, and lower alkoxy substituted with lower alkoxy. In one embodiment, R^{294} is selected from the group consisting of C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{1-3}

alkoxy, and C_{1-3} alkoxy substituted with C_{1-3} alkoxy. In one embodiment, R^{294} is selected from the group consisting of methyl, cyclopropyl, methoxy, ethoxy, and 2-methoxy-ethoxy.

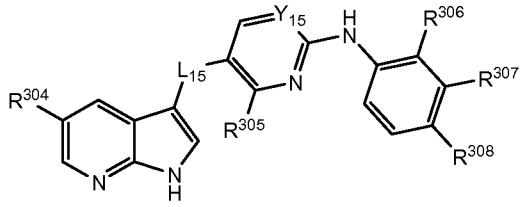
[0375] In some embodiments of compounds of Formula Iyy, further to any of the above embodiments of Formula Iyy, R^{295} and R^{296} are hydrogen and R^{297} is selected from the group consisting of fluoro, chloro, -O-R^{300}, -S-R^{301}, -S(O_2)-R^{302}, and lower alkyl optionally substitituted with one or more R^{303}. In some embodiments of compounds of Formula Iyy, further to any of the above embodiments of Formula Iyy, R^{295} and R^{296} are hydrogen and R^{297} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl optionally substitituted with one or more fluoro or -OH. In some embodiments of compounds of Formula Iyy, further to any of the above embodiments of Formula Iyy, R^{295} and R^{296} are hydrogen and R^{297} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl.

[0376] In some embodiments of compounds of Formula Iyy, further to any of the above embodiments of Formula Iyy, R^{295} and R^{297} are hydrogen and R^{296} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iyy, further to any of the above embodiments of Formula Iyy, R^{295} and R^{297} are hydrogen and R^{296} is fluoro, chloro, lower alkyl or lower alkoxy.

[0377] In some embodiments of compounds of Formula Iyy, further to any of the above embodiments of Formula Iyy, R^{296} and R^{297} are hydrogen and R^{295} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iyy, further to any of the above embodiments of Formula Iyy, R^{296} and R^{297} are hydrogen and R^{295} is fluoro, chloro, lower alkyl or lower alkoxy.

[0378] In some embodiments of compounds of Formula Iyy, further to any of the above embodiments of Formula Iyy, R^{295} is hydrogen, R^{296} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{297} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iyy, further to any of the above embodiments of Formula Iyy, R^{295} is hydrogen, R^{296} is fluoro, chloro, lower alkyl or lower alkoxy and R^{297} is fluoro, chloro, lower alkyl or lower alkoxy. In some embodiments of compounds of Formula Iyy, further to any of the above embodiments of Formula Iyy, R^{295} is hydrogen, R^{296} is fluoro, chloro, or lower alkoxy and R^{297} is fluoro, chloro, or lower alkoxy.

[0379] In a fifty-first aspect, compounds of Formula I having the structure according to the following Formula Izz are provided:



Formula Izz

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

Y_{15} is –N= and R^{305} is hydrogen; or Y_{15} is-C(H)= and R^{305} is fluoro;

L_{15} is -C(H_2)- or -C(O)-;

R^{304} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

R^{306} and R^{307} are hydrogen and R^{308} is selected from the group consisting of fluoro, chloro, -O-R^{309}, -S-R^{310}, -S(O_2)-R^{311}, and lower alkyl optionally substitituted with one or more R^{312}; or

R^{306} and R^{308} are hydrogen and R^{307} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{307} and R^{308} are hydrogen and R^{306} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{306} is hydrogen, R^{307} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{308} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro;

R^{309}, R^{310} and R^{311} are lower alkyl optionally substituted with one or more fluoro; and

R^{312} is fluoro, -OH, or lower alkoxy optionally substituted with one or more fluoro.

[0380] In some embodiments of compounds of Formula Izz, R^{304} is hydrogen, chloro or lower alkyl. In one embodiment, R^{304} is chloro or C_{1-3} alkyl. In one embodiment, R^{304} is chloro or methyl.

[0381] In some embodiments of compounds of Formula Izz, further to any of the above embodiments of Formula Izz, R^{306} and R^{307} are hydrogen and R^{308} is selected from the group consisting of fluoro, chloro, -O-R^{309}, -S-R^{310}, -S(O_2)-R^{311}, and lower alkyl optionally substitituted with one or more R^{312}. In some embodiments of compounds of Formula Izz, further to any of the above embodiments of Formula Izz, R^{306} and R^{307} are hydrogen and R^{308} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl optionally substitituted with one or more fluoro or -OH. In some embodiments of compounds of Formula Izz, further to any of the above embodiments of Formula Izz, R^{306} and R^{307} are hydrogen and

R^{308} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl.

[0382] In some embodiments of compounds of Formula Izz, further to any of the above embodiments of Formula Izz, R^{306} and R^{308} are hydrogen and R^{307} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Izz, further to any of the above embodiments of Formula Izz, R^{306} and R^{308} are hydrogen and R^{307} is fluoro, chloro, lower alkyl or lower alkoxy.

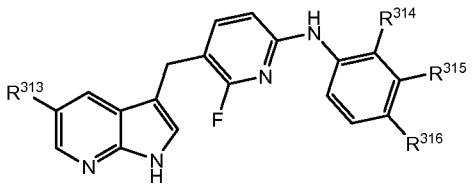
[0383] In some embodiments of compounds of Formula Izz, further to any of the above embodiments of Formula Izz, R^{307} and R^{308} are hydrogen and R^{306} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Izz, further to any of the above embodiments of Formula Izz, R^{307} and R^{308} are hydrogen and R^{306} is fluoro, chloro, lower alkyl or lower alkoxy.

[0384] In some embodiments of compounds of Formula Izz, further to any of the above embodiments of Formula Izz, R^{306} is hydrogen, R^{307} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{308} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Izz, further to any of the above embodiments of Formula Izz, R^{306} is hydrogen, R^{307} is fluoro, chloro, lower alkyl or lower alkoxy and R^{308} is fluoro, chloro, lower alkyl or lower alkoxy. In some embodiments of compounds of Formula Izz, further to any of the above embodiments of Formula Izz, R^{306} is hydrogen, R^{307} is fluoro, chloro, or lower alkoxy and R^{308} is fluoro, chloro, or lower alkoxy.

[0385] In some embodiments of compounds of Formula Izz, further to any of the above embodiments of Formula Izz, L_{15} is $-C(H_2)-$. In some embodiments of compounds of Formula Izz, further to any of the above embodiments of Formula Izz, L_{15} is -C(O)-.

[0386] In some embodiments of compounds of Formula Izz, further to any of the above embodiments of Formula Izz, Y_{15} is –N= and R^{305} is hydrogen. In some embodiments of compounds of Formula Izz, further to any of the above embodiments of Formula Izz, Y_{15} is -C(H)= and R^{305} is fluoro.

[0387] In a fifty-second aspect, compounds of Formula I having the structure according to the following Formula Iab are provided:



Formula Iab

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{313} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

R^{314} and R^{315} are hydrogen and R^{316} is selected from the group consisting of fluoro, chloro, -O-R^{317}, -S-R^{318}, -S(O_2)-R^{319}, and lower alkyl optionally substitituted with one or more R^{320}; or

R^{314} and R^{316} are hydrogen and R^{315} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{315} and R^{316} are hydrogen and R^{314} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{314} is hydrogen, R^{315} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{316} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro;

R^{317}, R^{318} and R^{319} are lower alkyl optionally substituted with one or more fluoro; and

R^{320} is fluoro, -OH, or lower alkoxy optionally substituted with one or more fluoro.

[0388] In some embodiments of compounds of Formula Iab, R^{313} is hydrogen, chloro or lower alkyl. In one embodiment, R^{313} is chloro or C_{1-3} alkyl. In one embodiment, R^{313} is chloro or methyl.

[0389] In some embodiments of compounds of Formula Iab, further to any of the above embodiments of Formula Iab, R^{314} and R^{315} are hydrogen and R^{316} is selected from the group consisting of fluoro, chloro, -O-R^{317}, -S-R^{318}, -S(O_2)-R^{319}, and lower alkyl optionally substitituted with one or more R^{320}. In some embodiments of compounds of Formula Iab, further to any of the above embodiments of Formula Iab, R^{314} and R^{315} are hydrogen and R^{316} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl optionally substitituted with one or more fluoro or -OH. In some embodiments of compounds of Formula Iab, further to any of the above embodiments of Formula Iab, R^{314} and R^{315} are hydrogen and R^{316} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl.

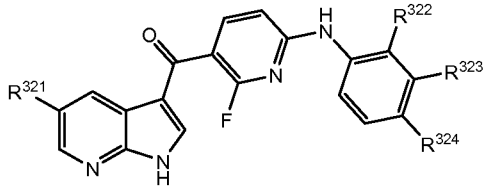
[0390] In some embodiments of compounds of Formula Iab, further to any of the above embodiments of Formula Iab, R^{314} and R^{316} are hydrogen and R^{315} is fluoro, chloro, lower alkyl

optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iab, further to any of the above embodiments of Formula Iab, R^{314} and R^{316} are hydrogen and R^{315} is fluoro, chloro, lower alkyl or lower alkoxy.

[0391] In some embodiments of compounds of Formula Iab, further to any of the above embodiments of Formula Iab, R^{315} and R^{316} are hydrogen and R^{314} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iab, further to any of the above embodiments of Formula Iab, R^{315} and R^{316} are hydrogen and R^{314} is fluoro, chloro, lower alkyl or lower alkoxy.

[0392] In some embodiments of compounds of Formula Iab, further to any of the above embodiments of Formula Iab, R^{314} is hydrogen, R^{315} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{316} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iab, further to any of the above embodiments of Formula Iab, R^{314} is hydrogen, R^{315} is fluoro, chloro, lower alkyl or lower alkoxy and R^{316} is fluoro, chloro, lower alkyl or lower alkoxy. In some embodiments of compounds of Formula Iab, further to any of the above embodiments of Formula Iab, R^{314} is hydrogen, R^{315} is fluoro, chloro, or lower alkoxy and R^{316} is fluoro, chloro, or lower alkoxy.

[0393] In a fifty-third aspect, compounds of Formula I having the structure according to the following Formula Iac are provided:



Formula Iac

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{321} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

R^{322} and R^{323} are hydrogen and R^{324} is selected from the group consisting of fluoro, chloro, $-O-R^{325}$, $-S-R^{326}$, $-S(O_2)-R^{327}$, and lower alkyl optionally substitituted with one or more R^{328}; or

R^{322} and R^{324} are hydrogen and R^{323} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{323} and R^{324} are hydrogen and R^{322} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{322} is hydrogen, R^{323} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{324} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro;

R^{325}, R^{326} and R^{327} are lower alkyl optionally substituted with one or more fluoro; and

R^{328} is fluoro, -OH, or lower alkoxy optionally substituted with one or more fluoro.

[0394] In some embodiments of compounds of Formula Iac, R^{321} is hydrogen, chloro or lower alkyl. In one embodiment, R^{321} is chloro or C_{1-3} alkyl. In one embodiment, R^{321} is chloro or methyl.

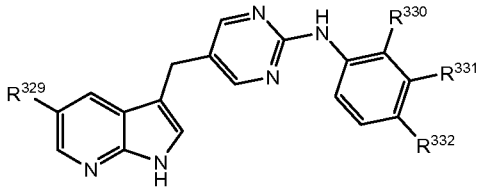
[0395] In some embodiments of compounds of Formula Iac, further to any of the above embodiments of Formula Iac, R^{322} and R^{323} are hydrogen and R^{324} is selected from the group consisting of fluoro, chloro, -O-R^{325}, -S-R^{326}, -S(O_2)-R^{327}, and lower alkyl optionally substitituted with one or more R^{328}. In some embodiments of compounds of Formula Iac, further to any of the above embodiments of Formula Iac, R^{322} and R^{323} are hydrogen and R^{324} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl optionally substitituted with one or more fluoro or -OH. In some embodiments of compounds of Formula Iac, further to any of the above embodiments of Formula Iac, R^{322} and R^{323} are hydrogen and R^{324} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl.

[0396] In some embodiments of compounds of Formula Iac, further to any of the above embodiments of Formula Iac, R^{322} and R^{324} are hydrogen and R^{323} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iac, further to any of the above embodiments of Formula Iac, R^{322} and R^{324} are hydrogen and R^{323} is fluoro, chloro, lower alkyl or lower alkoxy.

[0397] In some embodiments of compounds of Formula Iac, further to any of the above embodiments of Formula Iac, R^{323} and R^{324} are hydrogen and R^{322} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iac, further to any of the above embodiments of Formula Iac, R^{323} and R^{324} are hydrogen and R^{322} is fluoro, chloro, lower alkyl or lower alkoxy.

[0398] In some embodiments of compounds of Formula Iac, further to any of the above embodiments of Formula Iac, R^{322} is hydrogen, R^{323} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{324} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iac, further to any of the above embodiments of Formula Iac, R^{322} is hydrogen, R^{323} is fluoro, chloro, lower alkyl or lower alkoxy and R^{324} is fluoro, chloro, lower alkyl or lower alkoxy. In some embodiments of compounds of Formula Iac, further to any of the above embodiments of Formula Iac, R^{322} is hydrogen, R^{323} is fluoro, chloro, or lower alkoxy and R^{324} is fluoro, chloro, or lower alkoxy.

[0399] In a fifty-fourth aspect, compounds of Formula I having the structure according to the following Formula Iad are provided:



Formula Iad

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{329} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

R^{330} and R^{331} are hydrogen and R^{332} is selected from the group consisting of fluoro, chloro, -O-R^{333}, -S-R^{334}, -S(O_2)-R^{335}, and lower alkyl optionally substitituted with one or more R^{336}; or

R^{330} and R^{332} are hydrogen and R^{331} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{331} and R^{332} are hydrogen and R^{330} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{330} is hydrogen, R^{331} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{332} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro;

R^{333}, R^{334} and R^{335} are lower alkyl optionally substituted with one or more fluoro; and

R^{336} is fluoro, -OH, or lower alkoxy optionally substituted with one or more fluoro.

[0400] In some embodiments of compounds of Formula Iad, R^{329} is hydrogen, chloro or lower alkyl. In one embodiment, R^{329} is chloro or C_{1-3} alkyl. In one embodiment, R^{329} is chloro or methyl.

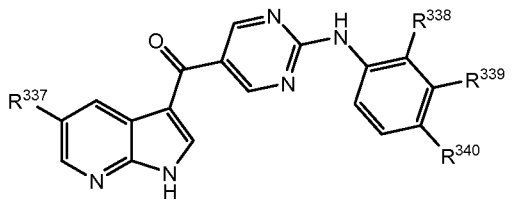
[0401] In some embodiments of compounds of Formula Iad, further to any of the above embodiments of Formula Iad, R^{330} and R^{331} are hydrogen and R^{332} is selected from the group consisting of fluoro, chloro, -O-R^{333}, -S-R^{334}, -S(O_2)-R^{335}, and lower alkyl optionally substitituted with one or more R^{336}. In some embodiments of compounds of Formula Iad, further to any of the above embodiments of Formula Iad, R^{330} and R^{331} are hydrogen and R^{332} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl optionally substitituted with one or more fluoro or -OH. In some embodiments of compounds of Formula Iad, further to any of the above embodiments of Formula Iad, R^{330} and R^{331} are hydrogen and R^{332} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl.

[0402] In some embodiments of compounds of Formula Iad, further to any of the above embodiments of Formula Iad, R^{330} and R^{332} are hydrogen and R^{331} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iad, further to any of the above embodiments of Formula Iad, R^{330} and R^{332} are hydrogen and R^{331} is fluoro, chloro, lower alkyl or lower alkoxy.

[0403] In some embodiments of compounds of Formula Iad, further to any of the above embodiments of Formula Iad, R^{331} and R^{332} are hydrogen and R^{330} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iad, further to any of the above embodiments of Formula Iad, R^{331} and R^{332} are hydrogen and R^{330} is fluoro, chloro, lower alkyl or lower alkoxy.

[0404] In some embodiments of compounds of Formula Iad, further to any of the above embodiments of Formula Iad, R^{330} is hydrogen, R^{331} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{332} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iad, further to any of the above embodiments of Formula Iad, R^{330} is hydrogen, R^{331} is fluoro, chloro, lower alkyl or lower alkoxy and R^{332} is fluoro, chloro, lower alkyl or lower alkoxy. In some embodiments of compounds of Formula Iad, further to any of the above embodiments of Formula Iad, R^{330} is hydrogen, R^{331} is fluoro, chloro, or lower alkoxy and R^{332} is fluoro, chloro, or lower alkoxy.

[0405] In a fifty-fifth aspect, compounds of Formula I having the structure according to the following Formula Iae are provided:



Formula Iae

or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

R^{337} is hydrogen, fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

R^{338} and R^{339} are hydrogen and R^{340} is selected from the group consisting of fluoro, chloro, -O-R^{341}, -S-R^{342}, -S(O_2)-R^{343}, and lower alkyl optionally substitituted with one or more R^{344}; or

R^{338} and R^{340} are hydrogen and R^{339} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{339} and R^{340} are hydrogen and R^{338} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro; or

R^{338} is hydrogen, R^{339} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{340} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro;

R^{341}, R^{342} and R^{343} are lower alkyl optionally substituted with one or more fluoro; and

R^{344} is fluoro, -OH, or lower alkoxy optionally substituted with one or more fluoro.

[0406] In some embodiments of compounds of Formula Iae, R^{337} is hydrogen, chloro or lower alkyl. In one embodiment, R^{337} is chloro or C_{1-3} alkyl. In one embodiment, R^{337} is chloro or methyl.

[0407] In some embodiments of compounds of Formula Iae, further to any of the above embodiments of Formula Iae, R^{338} and R^{339} are hydrogen and R^{340} is selected from the group consisting of fluoro, chloro, -O-R^{341}, -S-R^{342}, -S(O_2)-R^{343}, and lower alkyl optionally substitituted with one or more R^{344}. In some embodiments of compounds of Formula Iae, further to any of the above embodiments of Formula Iae, R^{338} and R^{339} are hydrogen and R^{340} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl optionally substitituted with one or more fluoro or -OH. In some embodiments of compounds of Formula Iae, further to any of the above embodiments of Formula Iae, R^{338} and R^{339} are hydrogen and R^{340} is selected from the group consisting of fluoro, chloro, lower alkoxy, lower alkylthio, lower alkylsulfonyl, and lower alkyl.

[0408] In some embodiments of compounds of Formula Iae, further to any of the above embodiments of Formula Iae, R^{338} and R^{340} are hydrogen and R^{339} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iae, further to any of the above embodiments of Formula Iae, R^{338} and R^{340} are hydrogen and R^{339} is fluoro, chloro, lower alkyl or lower alkoxy.

[0409] In some embodiments of compounds of Formula Iae, further to any of the above embodiments of Formula Iae, R^{339} and R^{340} are hydrogen and R^{338} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iae, further to any of the above embodiments of Formula Iae, R^{339} and R^{340} are hydrogen and R^{338} is fluoro, chloro, lower alkyl or lower alkoxy.

[0410] In some embodiments of compounds of Formula Iae, further to any of the above embodiments of Formula Iae, R^{338} is hydrogen, R^{339} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro and R^{340} is fluoro, chloro, lower alkyl optionally substitituted with one or more fluoro, or lower alkoxy optionally substitituted with one or more fluoro. In some embodiments of compounds of Formula Iae, further to any of the above embodiments of Formula Iae, R^{338} is hydrogen, R^{339} is fluoro, chloro, lower alkyl or lower alkoxy and R^{340} is fluoro, chloro, lower alkyl or lower alkoxy. In some embodiments of compounds of Formula Iae, further to any of the above embodiments of Formula Iae, R^{338} is hydrogen, R^{339} is fluoro, chloro, or lower alkoxy and R^{340} is fluoro, chloro, or lower alkoxy.

[0411] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of those set forth in Table 1.

Table 1

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclohexyl-amine (**P-3001**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclopentyl-amine (**P-3003**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4,4-difluoro-cyclohexyl)-amine (**P-3004**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclopropyl-amine (**P-3005**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cycloheptyl-amine (**P-3006**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclobutyl-amine (**P-3007**),
Cyclohexyl-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3008**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methyl-cyclohexyl)-amine

(**P-3009**),
(4-Fluoro-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3010**),
(4-Chloro-phenyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3011**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine (**P-3012**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(4,4-difluoro-cyclohexyl)-amine (**P-3013**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-phenyl)-amine (**P-3014**),
(2-Chloro-phenyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3015**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-phenyl)-amine (**P-3016**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-phenyl)-amine (**P-3017**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-yl)-amine (**P-3018**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-3019**),
(6-Methoxy-pyridin-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3020**),
(4-Methoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3021**),
(4-Fluoro-3-methoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3022**),
(3-Fluoro-4-methoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3023**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-propoxy-phenyl)-amine (**P-3024**),
(4-Ethyl-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3025**),
(4-Ethoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3026**),
(6-Ethoxy-pyridin-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3027**),

[5-(4-Fluoro-phenyl)-2H-pyrazol-3-yl]-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3028**),
(5-tert-Butyl-2H-pyrazol-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3029**),
(4-tert-Butyl-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3030**),
1,1,1,3,3,3-Hexafluoro-2-{4-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-ylamino]-phenyl}-propan-2-ol (**P-3031**),
(5-Cyclopropyl-2H-pyrazol-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3032**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methylsulfanyl-phenyl)-amine (**P-3033**),
(4-Methanesulfonyl-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3034**),
(1-Ethyl-1H-pyrazol-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3035**),
(1-Ethyl-1H-pyrazol-4-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3036**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-trifluoromethyl-2H-pyrazol-3-yl)-amine (**P-3037**),
(5-Isopropoxy-2H-pyrazol-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3038**),
(6-Ethoxy-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3039**),
[2-Fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3040**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-3041**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-3042**),
[2-Fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3043**),
(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-3044**),
[6-(6-Ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3045**),
(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-

amine (**P-3048**),
[6-(6-Ethyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3049**),
(6-Cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3050**),
[6-(6-Cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3051**),
[6-(6-Cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3052**),
(6-Cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3053**),
[6-Fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4001**),
[6-Fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4002**),
(6-Chloro-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4003**),
(6-Cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4004**),
(6-Ethoxy-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4005**),
(6-Ethoxy-pyridin-3-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4006**),
(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4007**),
(6-Ethoxy-pyridin-3-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4008**),
(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4009**),
[6-Fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-4010**),
(1-Ethyl-1H-pyrazol-4-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4011**),
[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(1-ethyl-1H-pyrazol-4-yl)-amine (**P-4012**),
(1-Ethyl-1H-pyrazol-4-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4013**),

(1-Ethyl-1H-pyrazol-4-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4014**),
{6-Fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-(6-methyl-pyridin-3-yl)-amine (**P-4015**),
(6-Ethyl-pyridin-3-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4016**),
[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-4017**),
[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4018**),
{6-Fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-(6-methoxy-pyridin-3-yl)-amine (**P-4019**),
(6-Bromo-pyridin-3-yl)-[5-(4-ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-amine (**P-4020**),
[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-pyridin-3-yl-amine (**P-4021**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-4022**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4023**),
[6-(6-Ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**P-4024**),
(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-4025**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-ethoxy-pyridin-3-yl)-amine (**P-4026**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-(6-ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-methanone (**P-4027**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-ethyl-pyridin-3-yl)-amine (**P-4028**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-(6-ethyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-methanone (**P-4029**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-4030**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-4031**),
[6-(6-Ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-

methanone (**P-4032**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(1-ethyl-1H-pyrazol-4-yl)-amine (**P-4036**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-(1-ethyl-1H-pyrazol-4-ylamino)-2-fluoro-pyridin-3-yl]-methanone (**P-4037**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-methyl-pyridin-3-yl)-amine (**P-4038**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(5-methyl-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-4039**),
[6-(6-Cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**P-4040**),
(6-Cyclopropyl-pyridin-3-yl)-[5-(4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-amine (**P-4041**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6,7-dihydro-5H-[1]pyrindin-3-yl)-amine (**P-4042**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-(6,7-dihydro-5H-[1]pyrindin-3-ylamino)-2-fluoro-pyridin-3-yl]-methanone (**P-4043**),
(6-Cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4044**),
[6-(6-Cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**P-4045**),
(4-amino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-chloro-6-[(4,4-difluorocyclohexyl)amino]-3-pyridyl]methanone (**P-4046**),
[2-chloro-6-[(4,4-difluorocyclohexyl)amino]-3-pyridyl]-[4-(2-methylprop-1-enylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4047**),
(4-amino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]methanone (**P-4048**),
[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[(2-hydroxy-2-methyl-propyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4049**),
[2-chloro-6-[(4,4-difluorocyclohexyl)amino]-3-pyridyl]-[4-(ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4050**),
[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]-[4-(ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4051**),
[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]-[4-(2,2,2-trifluoroethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4052**),
[4-(cyclopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(4,4-difluorocyclohexyl)amino]-5-

fluoro-3-pyridyl]methanone (**P-4053**),
[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4054**),
[4-(tert-butylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]methanone (**P-4055**),
[4-[(4,4-difluorocyclohexyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]methanone (**P-4056**),
[2-chloro-6-[(4,4-difluorocyclohexyl)amino]-3-pyridyl]-[4-(2,2,2-trifluoroethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4057**),
[2-chloro-6-[(4,4-difluorocyclohexyl)amino]-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4058**),
[2-chloro-6-[(4,4-difluorocyclohexyl)amino]-3-pyridyl]-[4-(cyclopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4059**),
[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-(ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4060**),
[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-(2,2,2-trifluoroethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4061**),
[4-(cyclopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]methanone (**P-4062**),
[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4063**),
[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[(2-hydroxy-2-methyl-propyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4064**),
(4-amino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]methanone (**P-4065**),
[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-(isopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4066**),
[4-(cyclopropylmethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]methanone (**P-4067**),
[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-(propylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4068**),
[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-(1-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4069**),
[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]-(4-morpholino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**P-4070**),

[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-[[6-(trifluoromethyl)-3-pyridyl]methylamino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4071**),
[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-[[(1S)-1-(4-fluorophenyl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4072**),
[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-(tetrahydrofuran-2-ylmethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4073**),
[4-[(1-ethyl-4-piperidyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]methanone (**P-4074**),
[4-(cyclopentylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]methanone (**P-4075**),
[4-(cyclobutylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]methanone (**P-4076**),
[4-(1-ethylpropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]methanone (**P-4077**),
[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-(sec-butylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4078**),
[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-(3-methoxypropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4079**),
[4-(butylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]methanone (**P-4080**),
[4-(ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]methanone (**P-4081**),
[4-(cyclohexylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]methanone (**P-4082**),
[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4083**),
[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-(2,2,2-trifluoroethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4084**),
[2-methoxy-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4085**),
[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[(6-methyl-3-pyridyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4086**),
[6-[(4,4-difluorocyclohexyl)amino]-3-pyridyl]-[4-(2,2,2-trifluoroethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4087**),
[4-(cyclopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(4,4-difluorocyclohexyl)amino]-3-

pyridyl]methanone (**P-4088**),
[6-[(4,4-difluorocyclohexyl)amino]-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4089**),
[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-(2,2,2-trifluoroethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4090**),
[4-(cyclopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[[6-(trifluoromethyl)-3-pyridyl]amino]-3-pyridyl]methanone (**P-4091**),
[2-fluoro-6-[[6-(trifluoromethyl)-3-pyridyl]amino]-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4092**),
[4-(cyclopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]methanone (**P-4093**),
[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4094**),
[4-(cyclobutylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]methanone (**P-4095**),
[4-[(4,4-difluorocyclohexyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]methanone (**P-4096**),
[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1S)-1-(4-fluorophenyl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4097**),
[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-(3-methoxypropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4098**),
[4-(cyclopentylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]methanone (**P-4099**),
[4-(butylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]methanone (**P-4100**),
[6-(cyclohexylamino)-2-fluoro-3-pyridyl]-[4-(isopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4101**),
[6-(cyclohexylamino)-2-fluoro-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4102**),
[2-fluoro-6-[(5-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-(2,2,2-trifluoroethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4103**),
[4-(cyclohexylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(5-methoxy-3-pyridyl)amino]-3-pyridyl]methanone (**P-4104**),
[2-fluoro-6-[(5-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-(propylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4105**),

[2-fluoro-6-[(5-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-(isopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone **(P-4106),**

[4-(cyclopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(5-methoxy-3-pyridyl)amino]-3-pyridyl]methanone **(P-4107)**,

[2-fluoro-6-[(5-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone **(P-4108)**,

[2-chloro-6-(cyclohexylamino)-3-pyridyl]-[4-(isopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone **(P-4109)**,

[2-chloro-6-(cyclohexylamino)-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone **(P-4110)**,

[4-(cyclohexylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(6-methyl-3-pyridyl)amino]-3-pyridyl]methanone **(P-4111)**,

[2-fluoro-6-[(6-methyl-3-pyridyl)amino]-3-pyridyl]-[4-(2,2,2-trifluoroethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone **(P-4112)**,

[4-(cyclopropylmethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(6-methyl-3-pyridyl)amino]-3-pyridyl]methanone **(P-4113)**,

[2-fluoro-6-[(6-methyl-3-pyridyl)amino]-3-pyridyl]-[4-(propylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone **(P-4114)**,

[2-fluoro-6-[(6-methyl-3-pyridyl)amino]-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone **(P-4115)**,

[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-(tetrahydropyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone **(P-4116)**,

[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-(isopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone **(P-4117)**,

[4-(cyclopropylmethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]methanone **(P-4118)**,

[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-(2-methoxyethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone **(P-4119)**,

[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-(2,2,2-trifluoroethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone **(P-4120)**,

[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-(isobutylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone **(P-4121)**,

[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-(propylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4122**),

[4-(ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-

pyridyl]methanone (**P-4123**),
[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4124**),
[4-(cyclopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]methanone (**P-4125**),
[4-(cyclopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]methanone (**P-4126**),
N-cyclopropyl-5-[[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]methyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**P-4127**),
5-[[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]methyl]-N-(2,2,2-trifluoroethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**P-4128**),
N-cyclopropyl-5-[[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]methyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**P-4129**),
5-[[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]methyl]-N-(2,2,2-trifluoroethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**P-4130**),
5-[[6-(cyclohexylamino)-2-fluoro-3-pyridyl]methyl]-N-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**P-4131**),
[2-fluoro-6-[(6-methoxy-3-pyridyl)amino]-3-pyridyl]-[4-[[(1R)-1-(4-fluorophenyl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4132**),
[6-[(6-ethyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-1-(4-fluorophenyl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4133**),
[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4134**),
[4-(ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]methanone (**P-4135**),
[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]-[4-(isopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4136**),
[4-(cyclopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]methanone (**P-4137**),
[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]-[4-(2,2,2-trifluoroethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4138**),
[4-[[(1R)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]methanone (**P-4139**),
[4-[[(1S)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]methanone (**P-4140**),

[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]-[4-(methoxymethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4141**),
[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]-[4-(3-methoxypropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4142**),
[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]-[4-(tetrahydropyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4143**),
[4-(cyclobutylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]methanone (**P-4144**),
[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4145**),
[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4146**),
[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(propylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4147**),
[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(isopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4148**),
[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(2,2,2-trifluoroethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4149**),
[4-[[(1R)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]methanone (**P-4150**),
[4-[[(1S)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]methanone (**P-4151**),
[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(methoxymethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4152**),
[6-[(3,3-15difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(tetrahydropyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4153**),
[4-(cyclobutylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]methanone (**P-4154**),
[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(3-methoxypropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4155**),
[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-(3-methoxypropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4156**),
[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-(2-methoxyethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4157**),
[4-(cyclobutylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]methanone (**P-4158**),

[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-(tetrahydropyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4159**),
[4-[[(1R)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]methanone (**P-4160**),
[4-[[(1S)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]methanone (**P-4161**),
[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-(ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4162**),
[4-(cyclobutylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]methanone (**P-4163**),
[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]-[4-(methoxymethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4164**),
[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]-[4-(3-methoxypropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4165**),
[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]-[4-(tetrahydropyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4166**),
[4-[[(1R)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]methanone (**P-4167**),
[4-[[(1S)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]methanone (**P-4168**),
[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1S)-1-methylpropyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4169**),
[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[(3-hydroxy-1-methyl-propyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4170**),
[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-1-(hydroxymethyl)propyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4171**),
4-[[5-[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]pyrrolidin-2-one (**P-4172**),
[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-2-hydroxy-1-methyl-ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4173**),
[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R,3R)-3-hydroxycyclohexyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4174**),
[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R,2R)-2-hydroxycyclopentyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4175**),
1-[3-[[5-[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]pyrrolidin-1-yl]ethanone (**P-4176**),

(2R)-2-[[5-[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]cyclohexanone (**P-4177**),
[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[(1,1-dioxothiolan-3-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4178**),
[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R,2R)-2-hydroxycyclohexyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4179**),
[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-2-methoxy-1-methyl-ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4180**),
4-[[5-[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]piperidin-2-one (**P-4181**),
[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-2,2,2-trifluoro-1-methyl-ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4182**),
4-[[5-[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-methyl-piperidin-2-one (**P-4183**),
[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[(1,1-dioxothian-3-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4184**),
1-cyclopropyl-4-[[5-[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]pyrrolidin-2-one (**P-4185**),
[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1S)-1-methylpropyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4186**),
[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[(3-hydroxy-1-methyl-propyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4187**),
[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-1-(hydroxymethyl)propyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4188**),
4-[[5-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]pyrrolidin-2-one (**P-4189**),
[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-2-hydroxy-1-methyl-ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4190**),
[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R,3R)-3-hydroxycyclohexyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4191**),
[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R,2R)-2-hydroxycyclopentyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4192**),
1-[3-[[5-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]pyrrolidin-1-yl]ethanone (**P-4193**),
(2R)-2-[[5-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]cyclohexanone (**P-4194**),

[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[(1,1-dioxothiolan-3-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4195**),
[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R,2R)-2-hydroxycyclohexyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4196**),
[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-2-methoxy-1-methyl-ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4197**),
4-[[5-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]piperidin-2-one (**P-4198**),
[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-2,2,2-trifluoro-1-methyl-ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4199**),
4-[[5-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-methyl-piperidin-2-one (**P-4200**),
[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[(1,1-dioxothian-3-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**P-4201**),
1-cyclopropyl-4-[[5-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]pyrrolidin-2-one (**P-4202**); and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0412] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclohexyl-amine (**P-3001**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclopentyl-amine (**P-3003**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4,4-difluoro-cyclohexyl)-amine (**P-3004**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclopropyl-amine (**P-3005**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cycloheptyl-amine (**P-3006**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclobutyl-amine (**P-3007**),
Cyclohexyl-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3008**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methyl-cyclohexyl)-amine (**P-3009**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(4,4-difluoro-cyclohexyl)-amine (**P-3013**), and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0413] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4,4-difluoro-cyclohexyl)-amine (**P-3004**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cycloheptyl-amine (**P-3006**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(4,4-difluoro-cyclohexyl)-amine (**P-3013**), and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0414] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:
(1-Ethyl-1H-pyrazol-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3035**),
(1-Ethyl-1H-pyrazol-4-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3036**),
(1-Ethyl-1H-pyrazol-4-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4011**),
[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(1-ethyl-1H-pyrazol-4-yl)-amine (**P-4012**),
(1-Ethyl-1H-pyrazol-4-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4013**),
(1-Ethyl-1H-pyrazol-4-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4014**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(1-ethyl-1H-pyrazol-4-yl)-amine (**P-4036**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-(1-ethyl-1H-pyrazol-4-ylamino)-2-fluoro-pyridin-3-yl]-methanone (**P-4037**), and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0415] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:
(4-Fluoro-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3010**),
(4-Chloro-phenyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3011**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine (**P-3012**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-phenyl)-amine (**P-3014**),
(2-Chloro-phenyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3015**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-phenyl)-amine (**P-3016**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-phenyl)-amine (**P-3017**),
(4-Methoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3021**),
(4-Fluoro-3-methoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3022**),
(3-Fluoro-4-methoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3023**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-propoxy-phenyl)-amine (**P-3024**),
(4-Ethyl-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3025**),
(4-Ethoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3026**),
(4-tert-Butyl-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3030**),
1,1,1,3,3,3-Hexafluoro-2-{4-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-ylamino]-phenyl}-propan-2-ol (**P-3031**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methylsulfanyl-phenyl)-amine (**P-3033**),
(4-Methanesulfonyl-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3034**), and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0416] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:
(4-Fluoro-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3010**),

(4-Chloro-phenyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3011**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine (**P-3012**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-phenyl)-amine (**P-3014**),
(4-Methoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3021**),
(4-Ethyl-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3025**),
(4-Ethoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3026**),
(4-tert-Butyl-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3030**),
1,1,1,3,3,3-Hexafluoro-2-{4-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-ylamino]-phenyl}-propan-2-ol (**P-3031**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methylsulfanyl-phenyl)-amine (**P-3033**), and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0417] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-yl)-amine (**P-3018**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-3019**),
(6-Methoxy-pyridin-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3020**),
(6-Ethoxy-pyridin-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3027**),
(6-Ethoxy-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3039**),
[2-Fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3040**),
[6-(6-Ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3045**),

[6-Fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4001**),
[6-Fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4002**),
(6-Ethoxy-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4005**),
(6-Ethoxy-pyridin-3-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4006**),
(6-Ethoxy-pyridin-3-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4008**),
[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4018**),
{6-Fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-(6-methoxy-pyridin-3-yl)-amine (**P-4019**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-4022**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4023**),
[6-(6-Ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**P-4024**),
(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-4025**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-ethoxy-pyridin-3-yl)-amine (**P-4026**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-(6-ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-methanone (**P-4027**),
[6-(6-Ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**P-4032**), and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0418] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-yl)-amine (**P-3018**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-3019**),

(6-Methoxy-pyridin-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3020**),
(6-Ethoxy-pyridin-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3027**),
(6-Ethoxy-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3039**),
[2-Fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3040**),
[6-(6-Ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3045**),
[6-Fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4001**),
(6-Ethoxy-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4005**),
(6-Ethoxy-pyridin-3-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4006**),
(6-Ethoxy-pyridin-3-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4008**),
[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4018**),
{6-Fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-(6-methoxy-pyridin-3-yl)-amine (**P-4019**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-4022**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4023**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-ethoxy-pyridin-3-yl)-amine (**P-4026**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-(6-ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-methanone (**P-4027**),
[6-(6-Ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**P-4032**), and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0419] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-3041**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-3042**),
[2-Fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3043**),
(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-3044**),
(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3048**),
[6-(6-Ethyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3049**),
(6-Cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3050**),
[6-(6-Cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3051**),
[6-(6-Cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3052**),
(6-Cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3053**),
(6-Cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4004**),
(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4007**),
(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4009**),
[6-Fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-4010**),
{6-Fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-(6-methyl-pyridin-3-yl)-amine (**P-4015**),
(6-Ethyl-pyridin-3-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4016**),
[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-4017**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-ethyl-pyridin-3-yl)-amine (**P-4028**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-(6-ethyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-

yl]-methanone (**P-4029**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-4030**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-4031**),
[6-(6-Cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**P-4040**),
(6-Cyclopropyl-pyridin-3-yl)-[5-(4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-amine (**P-4041**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6,7-dihydro-5H-[1]pyrindin-3-yl)-amine (**P-4042**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-(6,7-dihydro-5H-[1]pyrindin-3-ylamino)-2-fluoro-pyridin-3-yl]-methanone (**P-4043**),
(6-Cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4044**),
[6-(6-Cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**P-4045**), and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0420] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-3041**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-3042**),
[2-Fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3043**),
(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-3044**),
(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3048**),
[6-(6-Ethyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3049**),
(6-Cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3050**),
[6-(6-Cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-

yl)-methanone (**P-3051**),
[6-(6-Cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3052**),
(6-Cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3053**),
(6-Cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4004**),
(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4007**),
(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4009**),
[6-Fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-4010**),
(6-Ethyl-pyridin-3-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4016**),
[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-4017**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-ethyl-pyridin-3-yl)-amine (**P-4028**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-(6-ethyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-methanone (**P-4029**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-4030**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-4031**),
[6-(6-Cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**P-4040**),
(6-Cyclopropyl-pyridin-3-yl)-[5-(4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-amine (**P-4041**), and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0421] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:
(6-Chloro-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4003**),
(6-Bromo-pyridin-3-yl)-[5-(4-ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-

amine (**P-4020**),
[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-pyridin-3-yl-amine (**P-4021**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-methyl-pyridin-3-yl)-amine (**P-4038**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(5-methyl-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-4039**), and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0422] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-3019**),
(6-Methoxy-pyridin-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3020**),
(4-Methoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3021**),
[2-Fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3043**),
(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-3044**),
[6-(6-Ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3045**),
(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3048**),
[6-(6-Ethyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3049**),
(6-Ethoxy-pyridin-3-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4008**),
(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4009**),
(6-Ethyl-pyridin-3-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4016**),
[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4018**),
{6-Fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-(6-

methoxy-pyridin-3-yl)-amine (**P-4019**),
(6-Bromo-pyridin-3-yl)-[5-(4-ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-amine (**P-4020**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4023**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-ethoxy-pyridin-3-yl)-amine (**P-4026**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-ethyl-pyridin-3-yl)-amine (**P-4028**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-(6-ethyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-methanone (**P-4029**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-4030**), and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0423] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-3019**),
(6-Methoxy-pyridin-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3020**),
(4-Methoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3021**),
(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3048**),
(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4009**),
(6-Ethyl-pyridin-3-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4016**),
[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4018**),
(6-Bromo-pyridin-3-yl)-[5-(4-ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-amine (**P-4020**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-ethoxy-pyridin-3-yl)-amine (**P-4026**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-ethyl-pyridin-3-

yl)-amine (**P-4028**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-(6-ethyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-methanone (**P-4029**), and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0424] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:
[2-Fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3043**),
(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-3044**),
[6-(6-Ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3045**),
[6-(6-Ethyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3049**),
(6-Ethoxy-pyridin-3-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4008**),
{6-Fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-(6-methoxy-pyridin-3-yl)-amine (**P-4019**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4023**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-4030**), and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0425] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4,4-difluoro-cyclohexyl)-amine (**P-3004**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(4,4-difluoro-cyclohexyl)-amine (**P-3013**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-3041**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-3042**),

[6-Fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-4010**),
(1-Ethyl-1H-pyrazol-4-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4011**),
[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(1-ethyl-1H-pyrazol-4-yl)-amine (**P-4012**),
(1-Ethyl-1H-pyrazol-4-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4013**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(1-ethyl-1H-pyrazol-4-yl)-amine (**P-4036**), and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0426] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cycloheptyl-amine (**P-3006**),
(4-Fluoro-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3010**),
(4-Chloro-phenyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3011**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine (**P-3012**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-phenyl)-amine (**P-3014**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-yl)-amine (**P-3018**),
(4-Ethoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3026**),
(6-Ethoxy-pyridin-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3027**),
(1-Ethyl-1H-pyrazol-4-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3036**),
(6-Ethoxy-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3039**),
(1-Ethyl-1H-pyrazol-4-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4014**),
[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-

amine (**P-4017**), and
any salt, prodrug, solvate, tautomer, or stereoisomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt. In some embodiments, the invention provides a compound as set forth in Table 7 and any salt, solvate, prodrug, stereoisomer, or tautomer thereof. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0427] In reference to compounds 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 of Formula I described herein, it is understood (unless indicated otherwise) that a compound of Formula I includes all sub-embodiments thereof (Including any sub-generic Formulae Ia through Iae).

[0428] In a fifty-sixth aspect, a compound of Formula I is an inhibitor of Fms kinase 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 Fms 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 Fms kinase is >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 selective relative to Kit protein kinase, such that the ratio of IC_{50} for Kit kinase assessed comparably, divided by the IC_{50} for Fms kinase is >20, also >30, also >40, also >50, also >60, also >70, also >80, also >90, also >100.

[0429] In fifty-seventh aspect, a compound of Formula I is a Fms selective inhibitor, i.e. will selectively inhibit Fms kinase relative to Kit kinase. In some embodiments the compound 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 as determined in a generally accepted Fms kinase activity assay and when determined in a comparable generally accepted Kit kinase activity assay will have a ratio of IC_{50} for Kit kinase divided by the IC_{50} for Fms kinase of >20, also >30, also >40, also >50, also >60, also >70, also >80, also >90, also >100. In some embodiments, the compound is also selective relative to protein kinases other than Kit, such that the ratio of IC_{50} for another kinase assessed comparably, divided by the IC_{50} for Fms kinase is >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 Flt-3, CSK, Insulin receptor kinase, AMPK, PDGFR or VEGFR. In one embodiment, the Fms selective inhibitor

does not effectively cross the blood brain barrier. In one embodiment, the Fms selective inhibitor does effectively cross the blood brain barrier.

[0430] In a fifty-eighth aspect, a compound of Formula I is a dual Fms/Kit inhibitor, i.e. will be approximately equipotent with respect to inhibition of Fms kinase and Kit kinase. In some embodiments the compound 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 as determined in a generally accepted Fms kinase activity assay and 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 as determined in a comparable generally accepted Kit kinase activity assay, wherein the ratio of IC_{50} for Kit kinase divided by the IC_{50} for Fms kinase is in the range of 20 to 0.05, also 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 Fms kinase (and/or Kit kinase) is >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.

[0431] In a fifty-ninth aspect, a compound of Formula I is a dual Fms/Flt-3 inhibitor, i.e. will be approximately equipotent with respect to inhibition of Fms kinase and Flt-3 kinase. In some embodiments the compound 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 as determined in a generally accepted Fms kinase activity assay and 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 as determined in a comparable generally accepted Flt-3 kinase activity assay, wherein the ratio of IC_{50} for Flt-3 kinase divided by the IC_{50} for Fms kinase is in the range of 20 to 0.05, also 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 Fms kinase (and/or Flt3 kinase) is >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 dual Fms/Flt-3 inhibitor is selective with respect to Kit. In some embodiments, the dual Fms/Flt-3 inhibitor also inhibits Kit.

[0432] In a sixtieth aspect, a compound of Formula I is a dual Fms/Trk inhibitor, i.e. will be approximately equipotent with respect to inhibition of Fms kinase and Trk kinase. In some embodiments the compound 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 as determined in a generally accepted Fms kinase activity assay and 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 as determined in a

comparable generally accepted Trk kinase activity assay (including any one or more of TrkA, TrkB, and TrkC), wherein the ratio of IC_{50} for Trk kinase (at least one of TrkA, TrkB, and TrkC) divided by the IC_{50} for Fms kinase is in the range of 20 to 0.05, also 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 Fms kinase (and/or Trk kinase) is >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 dual Fms/Trk inhibitor is selective with respect to Kit. In some embodiments, the dual Fms/Trk inhibitor also inhibits Kit.

[0433] Further to any of the above mentioned aspects and embodiments, a compound of Formula I will also inhibit the effects of a mutation of the kinase, including, but not limited to, a mutation that is related to a disease state, such as a cancer.

[0434] In a sixty-first aspect, compositions are provided that include a therapeutically effective amount of any one or more compound(s) of Formula I and at least one pharmaceutically acceptable carrier, excipient, and/or diluent, including combinations of any two or more compounds of Formula I. The composition can further include a plurality of different pharmacologically active compounds, which can include a plurality of compounds of Formula I. In certain embodiments, the composition can include any one or more compound(s) of Formula I along with one or more compounds that are therapeutically effective for the same disease indication. In one aspect, the composition includes any one or more compound(s) of Formula I 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) of Formula I 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.

[0435] In a sixty-second aspect, methods are provided for treating a disease or condition related to any one or more of Fms protein kinase, Kit protein kinase, Flt3 protein kinase, and Trk protein kinase 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) of Formula I or a composition comprising any one or more compound(s) of Formula I. In certain embodiments, the method involves administering to the subject an effective amount of a compound of Formula I or a composition comprising a compound of Formula I in combination with one or more other therapies for the disease or condition.

[0436] In a sixty-third aspect, methods are provided for treating a disease or condition related to Fms protein kinase 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) of Formula I or a composition

comprising any one or more compound(s) of Formula I. In certain embodiments, the method involves administering to the subject an effective amount of a compound of Formula I or a composition comprising a compound of Formula I in combination with one or more other therapies for the disease or condition.

[0437] In a sixty-fourth aspect, methods are provided for treating a disease or condition related to Trk protein kinase 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) of Formula I or a composition comprising any one or more compound(s) of Formula I. In certain embodiments, the method involves administering to the subject an effective amount of a compound of Formula I or a composition comprising a compound of Formula I in combination with one or more other therapies for the disease or condition.

[0438] In a sixty-fifth aspect, methods are provided for treating a disease or condition related to Kit protein kinase 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) of Formula I or a composition comprising any one or more compound(s) of Formula I. In certain embodiments, the method involves administering to the subject an effective amount of a compound of Formula I or a composition comprising a compound of Formula I in combination with one or more other therapies for the disease or condition.

[0439] In a sixty-sixth aspect, methods are provided for treating a disease or condition related to Flt3 protein kinase 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) of Formula I or a composition comprising any one or more compound(s) of Formula I. In certain embodiments, the method involves administering to the subject an effective amount of a compound of Formula I or a composition comprising a compound of Formula I in combination with one or more other therapies for the disease or condition.

[0440] In a sixty-seventh aspect, methods are provided for treating a disease or condition related to Fms protein kinase and Kit protein kinase in an animal subject in need thereof, wherein the method involves administering to the subject an effective amount of any one or more dual Fms/Kit inhibitor(s) of Formula I or a composition comprising any one or more dual Fms/Kit inhibitor(s) of Formula I. In certain embodiments, the method involves administering to the subject an effective amount of a dual Fms/Kit inhibitor of Formula I or a composition comprising a dual Fms/Kit inhibitor of Formula I in combination with one or more other therapies for the disease or condition.

[0441] In a sixty-eighth aspect, methods are provided for treating a disease or condition related to Fms protein kinase and Flt-3 protein kinase in an animal subject in need thereof, wherein the method involves administering to the subject an effective amount of any one or more dual Fms/Flt-3 inhibitor(s) of Formula I or a composition comprising any one or more dual Fms/Flt-3 inhibitor(s) of Formula I. In certain embodiments, the method involves administering to the subject an effective amount of a dual Fms/Flt-3 inhibitor of Formula I or a composition comprising a dual Fms/Flt-3 inhibitor of Formula I in combination with one or more other therapies for the disease or condition.

[0442] In a sixty-ninth aspect, methods are provided for treating a disease or condition related to Fms protein kinase and Trk protein kinase in an animal subject in need thereof, wherein the method involves administering to the subject an effective amount of any one or more dual Fms/Trk inhibitor(s) of Formula I or a composition comprising any one or more dual Fms/Trk inhibitor(s) of Formula I. In certain embodiments, the method involves administering to the subject an effective amount of a dual Fms/Trk inhibitor of Formula I or a composition comprising a dual Fms/Trk inhibitor of Formula I in combination with one or more other therapies for the disease or condition.

[0443] In a seventieth 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 any one or more compound(s) of Formula I or a composition comprising any one or more compound(s) of Formula I, 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.

[0444] In a seventy-first 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 any one or more compound(s) of Formula I or a composition comprising any one or more compound(s) of Formula I, 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, 2'-F-ara-deoxyuridine, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, nelarabine, pemetrexed, pralatrexate, azathioprine, raltitrexed, tegafur-uracil, thioguanine, trimethoprim, trimetrexate, and vidarabine; an immunotherapy, including, but not limited to, alemtuzumab, bevacizumab, cetuximab, denileukin diftitox, galiximab, gemtuzumab, ofatumumab, panitumumab, pertuzumab, rituximab, tositumomab, trastuzumab, and 90 Y ibritumomab tiuxetan, ipilimumab, and tremelimumab; a hormone or hormone antagonist, including, but not limited to, anastrozole, androgens, bicalutamide, buserelin, Degarelix, diethylstilbestrol, exemestane, flutamide, fulvestrant, goserelin, idoxifene, letrozole, leuprolide, megestrol, nilutamide, raloxifene, tamoxifen, 4-hydroxytamoxifen, toremifene, and triptorelin; 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), pazopanib, seliciclib, sorafenib, sunitinib malate, AEE-788, BMS-599626, UCN-01 (7-hydroxystaurosporine), PLX4032, vatalanib, mTOR inhibitors (e.g. temsirolimus, everolimus, deforolimus, rapamycin), PI3K inhibitors (e.g. BEZ235, GDC-0941, XL147, XL765, CAL-101, PX-866, BGT226, GSK1059615), Cdk4 inhibitors (e.g. PD-332991, AG-024322), Akt inhibitors (e.g. GSK2110183, SR13668), MEK inhibitors (e.g. PD0325901, AZD8330, GSK1120212, RO4987655, RDEA119, XL518); a targeted signal transduction inhibitor including, but not limited to bortezomib, and geldanamycin; 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, COX-2 inhibitors (e.g. celecoxib, rofecoxib, valdecoxib, lumiracoxib, etoricoxib), Hsp90 inhibitors (e.g. tanespimycin) and farnesyltransferase inhibitors (e.g. tipifarnib).

[0445] In a seventy-second aspect, the invention provides kits that include any one or more compound(s) of Formula I or a composition comprising any one or more compound(s) of Formula I. 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 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.

[0446] In aspects and embodiments involving treatment or prophylaxis of a disease or condition with any one or more compound(s) of Formula I or a composition comprising any one or more compound(s) of Formula I, the invention provides methods for treating a disease or condition related to Kit in an animal 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 Kit activity (e.g. kinase activity). In some embodiments invention methods may involve administering to the subject suffering from or at risk of a disease or condition related to Kit an effective amount of any one or more compound(s) of Formula I or a composition comprising any one or more compound(s) of Formula I. In one embodiment, the disease related to Kit is selected from the group consisting of malignancies, including, but not limited to, mast cell tumors, small cell lung cancer, non-small cell lung cancer (NSCLC), testicular cancer, pancreatic cancer, breast cancer, prostate cancer, merkel cell carcinoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, gastrointestinal stromal tumors (GISTs), multiple myeloma, tumor angiogenesis, brain metastases, glioblastoma, astrocytoma, neuroblastoma, neurofibromatosis (including Schwann cell neoplasia associated with neurofibromatosis), acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, mastocytosis, melanoma, and canine mast cell tumors; cardiovascular disease, including but not limited to atherosclerosis, cardiomyopathy, heart failure, pulmonary arterial hypertension and pulmonary fibrosis; inflammatory and autoimmune indications, including, but not limited to, allergy, anaphylaxis, asthma, rheumatoid arthritis, allergic rhinitis,

multiple sclerosis, inflammatory bowel disease, transplant rejection, hypereosinophilia, urticaria and dermatitis; gastrointestinal indications, including but not limited to gastroesophageal reflux disease (GERD), esophagitis, and gastrointestinal tract ulcers; ophthalmic indications, including but not limited to uveitis and retinitis; and neurologic indications, including but not limited to migraine.

[0447] In aspects and embodiments involving treatment or prophylaxis of a disease or condition with any one or more compound(s) of Formula I or a composition comprising any one or more compound(s) of Formula I, the invention provides methods for treating a disease or condition related to Fms in an animal 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 Fms activity (e.g. kinase activity). In some embodiments, invention methods may involve administering to the subject suffering from or at risk of a disease or condition related to Fms an effective amount of any one or more compound(s) of Formula I or a composition comprising any one or more compound(s) of Formula I. In one embodiment, the disease related to Fms is selected from the group consisting of inflammatory and autoimmune indications, including, but not limited to, rheumatoid arthritis, osteoarthritis, psoriatic arthritis, psoriasis, dermatitis, ankylosing spondylitis, polymyositis, dermatomyositis, systemic sclerosis, juvenile idiopathic arthritis, polymyalgia rheumatica, Sjogren's disease, Langerhan's cell histiocytosis (LCH), Still's disease, inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic lupus erythematosis (SLE), immune thrombocytopenic purpura (ITP), myelopreparation for autologous transplantation, transplant rejection, chronic obstructive pulmonary disease (COPD), emphysema, Kawasaki's Disease, hemophagocytic syndrome (macrophage activation syndrome), multicentric reticulohistiocytosis, and atherosclerosis; metabolic disorders, including, but not limited to, Type I diabetes, Type II diabetes, insulin resistance, hyperglycemia, obesity, and lipolysis; disorders of bone structure, mineralization and bone formation and resorption, including, but not limited to, osteoporosis, osteodystrophy, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis (e.g. osteomyelitis), and peri-prosthetic or wear-debris-mediated osteolysis; kidney and genitourinary diseases, including, but not limited to, endometriosis, nephritis (e.g. glomerulonephritis, interstitial nephritis, Lupus nephritis), tubular necrosis, diabetes-associated renal complications (e.g. diabetic nephropathy), and renal hypertrophy; disorders of the nervous system, including, but not limited to, demyelinating disorders (e.g. multiple sclerosis, Charcot Marie Tooth syndrome), amyotrophic lateral sclerosis (ALS), myasthenia gravis, chronic demyelinating polyneuropathy, other demyelinating disorders, stroke, Alzheimer's disease and Parkinson's disease; pain, including, but not limited to, chronic pain, acute pain, inflammatory pain, neuropathic pain, bone pain; malignancies, including, but not limited to, multiple myeloma, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), lung cancer, pancreatic cancer, prostate cancer, breast cancer, ovarian cancer, neuroblastoma, sarcoma, osteosarcoma, giant cell

tumors, (e.g. giant cell tumor of bone, giant cell tumor of tendon sheath (TGCT)), pigmented villonodular synovitis (PVNS), tumor angiogenesis, melanoma, glioblastoma multiforme, glioma, other tumors of the central nervous system, brain metasteses, osteolytic bone metastases, metastasis of tumors to other tissues, and other chronic myeloproliferative diseases such as myelofibrosis; vasculitis, including but not limited to collagen vascular disease, polyarteritis nodosa, Behcet's disease, sarcoidosis, familiar Mediterranean fever, Churg-Strauss vasculitis, temporal arteritis, giant cell arteritis, Takayasu's arteritis; ophthalmic indications, including but not limited to uveitis, scleritis, retinitis, age related macular degeneration, choroidal neovascularization, diabetic retinopathy; inherited disorders, including but not limited to cherubism, neurofibromatosis; infectious disease indications, including but not limited to infections associated with human immunodeficiency virus, hepatitis B virus, hepatitis C virus, human granulocytic anaplasmosis; lysosomal storage disorders, including but not limited to Gaucher's disease, Fabry's disease, Niemann-Pick disease; gastrointestinal indications, including but not limited to liver cirrhosis; pulmonary indications, including but not limited to pulmonary fibrosis, acute lung injury (e.g. ventilator-induced, smoke- or toxin-induced); global ischemia, and surgical indications, including but not limited to (cardiopulmonary) bypass surgery, vascular surgery, and vascular grafts.

[0448] In aspects and embodiments involving treatment or prophylaxis of a disease or condition with the any one or more compound(s) of Formula I or a composition comprising any one or more compound(s) of Formula I, the invention provides methods for treating a disease or condition related to Flt-3 in an animal 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 Flt-3 activity (e.g. kinase activity). In some embodiments, invention methods may involve administering to the subject suffering from or at risk of a disease or condition related to Flt-3 an effective amount of any one or more compound(s) of Formula I or a composition comprising any one or more compound(s) of Formula I. In one embodiment, the disease related to Flt-3 is selected from the group consisting of malignancies, including, but not limited to, glioma, glioblastoma, brain metastases, lung cancer, breast cancer, colorectal cancer, prostate cancer, gastric cancer, esophageal cancer, pancreatic cancer, ovarian cancer, non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, acute lymphocytic leukemia, acute myeloid leukemia, acute myeloid leukemia with trilineage myelodysplasia, acute promyelocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, chronic neutrophilic leukemia, acute undifferentiated leukemia, anaplastic large-cell lymphoma, prolymphocyte leukemia, juvenile myelomonocyctic leukemia, adult T-cell acute lymphocytic leukemia, T-cell type acute lymphocytic leukemia, B-cell type acute lymphocytic leukemia, mixed lineage leukemia, multiple myeloma, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myeloblastic leukemia, chronic myelomonocytic leukemia; other

diseases including psoriasis, atopic dermatitis, axonal degeneration, acute transverse myelitis, amyotrophic lateral sclerosis, infantile spinal muscular atrophy, juvenile spinal muscular atrophy, Creutzfeldt- Jakob disease, subacute sclerosing panencephalitis, organ rejection, bone marrow transplant rejection, non-myeloablative bone marrow transplant rejection, ankylosing spondylitis, aplastic anemia, Behcet's disease, graft-versus-host disease, Graves' disease, autoimmune hemolytic anemia, Wegener's granulomatosis, hyper IgE syndrome, idiopathic thrombocytopenia purpura, Myasthenia gravis, type 1 diabetes mellitus, rheumatoid arthritis, Crohn's disease, multiple sclerosis, systemic lupus erythematosus, myelodysplastic syndrome, thrombocythemia, essential thrombocytosis, angiogenic myeloid metaplasia, myelofibrosis, myelofibrosis with myeloid metaplasia, chronic idiopathic myelofibrosis, polycythemia vera, anemia, leukopenia, neutropenia, thrombocytopenia, granulocytopenia, and pancytopenia.

[0449] In aspects and embodiments involving treatment or prophylaxis of a disease or condition with the any one or more compound(s) of Formula I or a composition comprising any one or more compound(s) of Formula I, the invention provides methods for treating a disease or condition related to Trk in an animal 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 Trk activity (e.g. kinase activity). In some embodiments, invention methods may involve administering to the subject suffering from or at risk of a disease or condition related to Trk an effective amount of any one or more compound(s) of Formula I or a composition comprising any one or more compound(s) of Formula I. In one embodiment, the disease related to Trk is selected from the group consisting of malignancies, including, but not limited to, prostate cancer, small cell lung cancer, non-small cell lung cancer, Wilms tumors, mesoblastic nephroma, infantile fibrosarcoma, neuroblastoma, brain cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, breast cancer, head and neck cancer, esophageal cancer, colorectal cancer, renal cancer, hepatocellular cancer, ovarian cancer, gynecological cancer, thyroid cancer, cervical cancer, ewings tumor, tumors of the central and peripheral nervous system, melanoma, multiple myeloma, acute myelogenous leukemia, and myeloid leukemia; neuropathies, including, but not limited to, stroke, multiple sclerosis, Parkinson's disease, Alzheimer's disease, transverse myelitis, and encephalitis; pain, including, but not limited to, chronic pain, acute pain, inflammatory pain, neuropathic pain, and pain associated with cancer, surgery, or bone fracture; bone-related diseases, including, but not limited to, metastatic bone disease, treatment-induced bone loss, osteoporosis, rheumatoid arthritis, ankylosing spondylitis, Paget's disease, and periodontal disease; other diseases, including, but not limited to, asthma, arthritis, diabetic retinopathy, macular degeneration, psoriasis, acute and chronic inflammation, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis,

fibrosarcoma, osteosarcoma, panic disorder, and infectious disease (e.g. Typanosoma cruzi infection (Chagas disease)).

[0450] In aspects and embodiments involving treatment or prophylaxis of a disease or condition, methods may involve administering an effective amount of any one or more compound(s) of Formula I or a composition comprising any one or more compound(s) of Formula I to a subject in need thereof suffering from or at risk of a disease or condition selected from the group consisting of rheumatoid arthiritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, systemic sclerosis, demyelinating disorders, multiple sclerosis, Charcot Marie Tooth syndrome, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, ulcerative colitis, Crohn's disease, immune thrombocytopenic purpura, atherosclerosis, systemic lupus erythematosis, myelopreparation for autologous transplantation, transplant rejection, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, renal hypertrophy, type I diabetes, acute pain, inflammatory pain, neuropathic pain, acute myeloid leukemia, melanoma, multiple myeloma, breast cancer, prostate cancer, pancreatic cancer, lung cancer, ovarian cancer, gliomas, glioblastomas, neurofibromatosis, osteolytic bone metastases, brain metastases, gastrointestinal stromal tumors, and giant cell tumors.

[0451] In aspects and embodiments involving treatment or prophylaxis of a disease or condition, methods may involve administering an effective amount of any one or more compound(s) of Formula I or a composition comprising any one or more compound(s) of Formula I to a subject in need thereof suffering from or at risk of a disease or condition selected from the group consisting of rheumatoid arthritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, multiple sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, renal hypertrophy, acute myeloid leukemia, melanoma, multiple myeloma, breast cancer, prostate cancer, pancreatic cancer, glioblastoma, neurofibromatosis, brain metastases, and gastrointestinal stromal tumors.

[0452] In aspects and embodiments involving treatment or prophylaxis of a disease or condition, methods may involve administering an effective amount of any one or more Kit inhibitor(s) of Formula I or a composition comprising any one or more Kit inhibitor(s) of Formula I to a subject in need thereof suffering from or at risk of a disease or condition selected from the group consisting of rheumatoid arthritis, gastrointestinal stromal tumors, melanoma and neurofibromatosis.

[0453] In aspects and embodiments involving treatment or prophylaxis of a disease or condition, methods may involve administering an effective amount of any one or more Fms selective inhibitor(s) of Formula I or a composition comprising any one or more Fms selective inhibitor(s) of Formula I to a subject in need thereof suffering from or at risk of a disease or condition selected from the group consisting of multiple sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia,

rheumatoid arthritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, glomerulonephritis, interstitial nephritis, Lupus nephritis, diabetic nephropathy, and renal hypertrophy.

[0454] In aspects and embodiments involving treatment or prophylaxis of a disease or condition, methods may involve administering an effective amount of any one or more Fms selective inhibitor(s) of Formula I or a composition comprising any one or more Fms selective inhibitor(s) of Formula I to a subject in need thereof suffering from or at risk of a disease or condition selected from the group consisting of multiple sclerosis, Alzheimer's disease, Parkinson's disease, and global ischemia, wherein the one or more Fms selective inhibitor(s) does effectively cross the blood brain barrier.

[0455] In aspects and embodiments involving treatment or prophylaxis of a disease or condition, methods may involve administering an effective amount of any one or more Fms selective inhibitor(s) of Formula I or a composition comprising any one or more Fms selective inhibitor(s) of Formula I to a subject in need thereof suffering from or at risk of a disease or condition selected from the group consisting of rheumatoid arthritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, glomerulonephritis, interstitial nephritis, Lupus nephritis, diabetic nephropathy, and renal hypertrophy, wherein the one or more Fms selective inhibitor(s) does not effectively cross the blood brain barrier.

[0456] In aspects and embodiments involving treatment or prophylaxis of a disease or condition, methods may involve administering an effective amount of any one or more dual Fms/Kit inhibitor(s) of Formula I or a composition comprising any one or more dual Fms/Kit inhibitor(s) of Formula I to a subject in need thereof suffering from or at risk of a disease or condition selected from the group consisting of breast cancer, prostate cancer, multiple myeloma, melanoma, acute myeloid leukemia, glioblastoma, brain metastases, neurofibromatosis, gastrointestinal stromal tumors, rheumatoid arthritis, and multiple sclerosis.

[0457] In aspects and embodiments involving treatment or prophylaxis of a disease or condition, methods may involve administering an effective amount of any one or more dual Fms/Flt-3 inhibitor(s) of Formula I or a composition comprising any one or more dual Fms/Flt-3 inhibitor(s) of Formula I to a subject in need thereof suffering from or at risk of a disease or condition selected from the group consisting of breast cancer, prostate cancer, multiple myeloma, melanoma, acute myeloid leukemia, glioblastoma, brain metastases, neurofibromatosis, gastrointestinal stromal tumors, rheumatoid arthritis, and multiple sclerosis, preferably wherein the disease is acute myeloid leukemia.

[0458] In aspects and embodiments involving treatment or prophylaxis of a disease or condition, methods may involve administering an effective amount of any one or more dual Fms/Trk inhibitor(s) of Formula I or a composition comprising any one or more dual Fms/Trk inhibitor(s) of Formula I to a

subject in need thereof suffering from or at risk of a disease or condition selected from the group consisting of pancreatic cancer, prostate cancer, and multiple myeloma.

[0459] In a seventy-third aspect, any one or more compound(s) of Formula I can be used in the preparation of a medicament for the treatment of a disease or condition related to Kit selected from the group consisting of malignancies, including, but not limited to, mast cell tumors, small cell lung cancer, non-small cell lung cancer (NSCLC), testicular cancer, pancreatic cancer, breast cancer, prostate cancer, merkel cell carcinoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, gastrointestinal stromal tumors (GISTs), multiple myeloma, tumor angiogenesis, brain metastases, glioblastoma, astrocytoma, neuroblastoma, neurofibromatosis (including Schwann cell neoplasia associated with neurofibromatosis), acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, mastocytosis, melanoma, and canine mast cell tumors; cardiovascular disease, including but not limited to atherosclerosis, cardiomyopathy, heart failure, pulmonary arterial hypertension and pulmonary fibrosis; inflammatory and autoimmune indications, including, but not limited to, allergy, anaphylaxis, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel disease, transplant rejection, hypereosinophilia, urticaria and dermatitis; gastrointestinal indications, including but not limited to gastroesophageal reflux disease (GERD), esophagitis, and gastrointestinal tract ulcers; ophthalmic indications, including but not limited to uveitis and retinitis; and neurologic indications, including but not limited to migraine.

[0460] In a seventy-fourth aspect, any one or more compound(s) of Formula I can be used in the preparation of a medicament for the treatment of a disease or condition related to Fms selected from the group consisting of inflammatory and autoimmune indications, including, but not limited to, rheumatoid arthritis, osteoarthritis, psoriatic arthritis, psoriasis, dermatitis, ankylosing spondylitis, polymyositis, dermatomyositis, systemic sclerosis, juvenile idiopathic arthritis, polymyalgia rheumatica, Sjogren's disease, Langerhan's cell histiocytosis (LCH), Still's disease, inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic lupus erythematosis (SLE), immune thrombocytopenic purpura (ITP), myelopreparation for autologous transplantation, transplant rejection, chronic obstructive pulmonary disease (COPD), emphysema, Kawasaki's Disease, hemophagocytic syndrome (macrophage activation syndrome), multicentric reticulohistiocytosis, and atherosclerosis; metabolic disorders, including, but not limited to, Type I diabetes, Type II diabetes, insulin resistance, hyperglycemia, obesity, and lipolysis; disorders of bone structure, mineralization and bone formation and resorption, including, but not limited to, osteoporosis, osteodystrophy, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis (e.g. osteomyelitis), and peri-prosthetic or wear-debris-mediated osteolysis; kidney and genitourinary diseases, including, but not limited to, endometriosis, nephritis (e.g. glomerulonephritis, interstitial

nephritis, Lupus nephritis), tubular necrosis, diabetes-associated renal complications (e.g. diabetic nephropathy), and renal hypertrophy; disorders of the nervous system, including, but not limited to, demyelinating disorders (e.g. multiple sclerosis, Charcot Marie Tooth syndrome), amyotrophic lateral sclerosis (ALS), myasthenia gravis, chronic demyelinating polyneuropathy, other demyelinating disorders, stroke, Alzheimer's disease and Parkinson's disease; pain, including, but not limited to, chronic pain, acute pain, inflammatory pain, neuropathic pain, bone pain; malignancies, including, but not limited to, multiple myeloma, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), lung cancer, pancreatic cancer, prostate cancer, breast cancer, ovarian cancer, neuroblastoma, sarcoma, osteosarcoma, giant cell tumors, (e.g. giant cell tumor of bone, giant cell tumor of tendon sheath (TGCT)), pigmented villonodular synovitis (PVNS), tumor angiogenesis, melanoma, glioblastoma multiforme, glioma, other tumors of the central nervous system, brain metasteses, osteolytic bone metastases, metastasis of tumors to other tissues, and other chronic myeloproliferative diseases such as myelofibrosis; vasculitis, including but not limited to collagen vascular disease, polyarteritis nodosa, Behcet's disease, sarcoidosis, familiar Mediterranean fever, Churg-Strauss vasculitis, temporal arteritis, giant cell arteritis, Takayasu's arteritis; ophthalmic indications, including but not limited to uveitis, scleritis, retinitis, age related macular degeneration, choroidal neovascularization, diabetic retinopathy; inherited disorders, including but not limited to cherubism, neurofibromatosis; infectious disease indications, including but not limited to infections associated with human immunodeficiency virus, hepatitis B virus, hepatitis C virus, human granulocytic anaplasmosis; lysosomal storage disorders, including but not limited to Gaucher's disease, Fabry's disease, Niemann-Pick disease; gastrointestinal indications, including but not limited to liver cirrhosis; pulmonary indications, including but not limited to pulmonary fibrosis, acute lung injury (e.g. ventilator-induced, smoke- or toxin-induced); global ischemia, and surgical indications, including but not limited to (cardiopulmonary) bypass surgery, vascular surgery, and vascular grafts.

[0461] In a seventy-fifth aspect, any one or more compound(s) of Formula I can be used in the preparation of a medicament for the treatment of a disease or condition related to Flt-3 selected from the group consisting of malignancies, including, but not limited to, glioma, glioblastoma, brain metastases, lung cancer, breast cancer, colorectal cancer, prostate cancer, gastric cancer, esophageal cancer, pancreatic cancer, ovarian cancer, non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, acute lymphocytic leukemia, acute myeloid leukemia, acute myeloid leukemia with trilineage myelodysplasia, acute promyelocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, chronic neutrophilic leukemia, acute undifferentiated leukemia, anaplastic large-cell lymphoma, prolymphocyte leukemia, juvenile myelomonocyctic leukemia, adult T-cell acute lymphocytic leukemia, T-cell type acute lymphocytic leukemia, B-cell type acute lymphocytic leukemia, mixed lineage leukemia, multiple myeloma, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myeloblastic leukemia, chronic myelomonocytic leukemia; other

diseases including psoriasis, atopic dermatitis, axonal degeneration, acute transverse myelitis, amyotrophic lateral sclerosis, infantile spinal muscular atrophy, juvenile spinal muscular atrophy, Creutzfeldt- Jakob disease, subacute sclerosing panencephalitis, organ rejection, bone marrow transplant rejection, non-myeloablative bone marrow transplant rejection, ankylosing spondylitis, aplastic anemia, Behcet's disease, graft-versus-host disease, Graves' disease, autoimmune hemolytic anemia, Wegener's granulomatosis, hyper IgE syndrome, idiopathic thrombocytopenia purpura, Myasthenia gravis, type 1 diabetes mellitus, rheumatoid arthritis, Crohn's disease, multiple sclerosis, systemic lupus erythematosus, myelodysplastic syndrome, thrombocythemia, essential thrombocytosis, angiogenic myeloid metaplasia, myelofibrosis, myelofibrosis with myeloid metaplasia, chronic idiopathic myelofibrosis, polycythemia vera, anemia, leukopenia, neutropenia, thrombocytopenia, granulocytopenia, and pancytopenia.

[0462] In a seventy-sixth aspect, any one or more compound(s) of Formula I can be used in the preparation of a medicament for the treatment of a disease or condition related to Trk selected from the group consisting of malignancies, including, but not limited to, prostate cancer, small cell lung cancer, non-small cell lung cancer, Wilms tumors, mesoblastic nephroma, infantile fibrosarcoma, neuroblastoma, brain cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, breast cancer, head and neck cancer, esophageal cancer, colorectal cancer, renal cancer, hepatocellular cancer, ovarian cancer, gynecological cancer, thyroid cancer, cervical cancer, ewings tumor, tumors of the central and peripheral nervous system, melanoma, multiple myeloma, acute myelogenous leukemia, and myeloid leukemia; neuropathies, including, but not limited to, stroke, multiple sclerosis, Parkinson's disease, Alzheimer's disease, transverse myelitis, and encephalitis; pain, including, but not limited to, chronic pain, acute pain, inflammatory pain, neuropathic pain, and pain associated with cancer, surgery, or bone fracture; bone-related diseases, including, but not limited to, metastatic bone disease, treatment-induced bone loss, osteoporosis, rheumatoid arthritis, ankylosing spondylitis, Paget's disease, and periodontal disease; other diseases, including, but not limited to, asthma, arthritis, diabetic retinopathy, macular degeneration, psoriasis, acute and chronic inflammation, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, fibrosarcoma, osteosarcoma, panic disorder, and infectious disease (e.g. Typanosoma cruzi infection (Chagas disease)).

[0463] In a seventy-seventh aspect, any one or more compound(s) of Formula I can be used in the preparation of a medicament for the treatment of a disease or condition selected from the group consisting of rheumatoid arthiritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, systemic sclerosis, demyelinating disorders, multiple sclerosis, Charcot Marie Tooth syndrome, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, ulcerative colitis, Crohn's disease, immune thrombocytopenic purpura, atherosclerosis, systemic lupus erythematosis,

myelopreparation for autologous transplantation, transplant rejection, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, renal hypertrophy, type I diabetes, acute pain, inflammatory pain, neuropathic pain, acute myeloid leukemia, melanoma, multiple myeloma, breast cancer, prostate cancer, pancreatic cancer, lung cancer, ovarian cancer, gliomas, glioblastomas, neurofibromatosis, osteolytic bone metastases, brain metastases, gastrointestinal stromal tumors, and giant cell tumors.

[0464] In a seventy-eighth aspect, any one or more compound(s) of Formula I can be used in the preparation of a medicament for the treatment of a disease or condition selected from the group consisting of rheumatoid arthiritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, multiple sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, renal hypertrophy, acute myeloid leukemia, melanoma, multiple myeloma, breast cancer, prostate cancer, pancreatic cancer, glioblastoma, neurofibromatosis, brain metastases, and gastrointestinal stromal tumors.

[0465] In a seventy-ninth aspect, one or more compounds as described herein that are Kit inhibitors can be used in the preparation of a medicament for the treatment of rheumatoid arthritis, gastrointestinal stromal tumors, melanoma or neurofibromatosis.

[0466] In an eightieth aspect, one or more compounds as described herein that are Fms selective inhibitors can be used in the preparation of a medicament for the treatment of multiple sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, rheumatoid arthritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, glomerulonephritis, interstitial nephritis, Lupus nephritis, diabetic nephropathy, or renal hypertrophy.

[0467] In an eighty-first aspect, one or more compounds as described herein that are Fms selective inhibitors that effectively cross the blood brain barrier can be used in the preparation of a medicament for the treatment of multiple sclerosis, glioblastoma, Alzheimer's disease, Parkinson's disease, or global ischemia.

[0468] In an eighty-second aspect, one or more compounds as described herein that are Fms selective inhibitors that do not effectively cross the blood brain barrier can be used in the preparation of a medicament for the treatment of rheumatoid arthritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, glomerulonephritis, interstitial nephritis, Lupus nephritis, diabetic nephropathy, or renal hypertrophy.

[0469] In an eighty-third aspect, one or more compounds as described herein that are dual Fms/Kit inhibitors can be used in the preparation of a medicament for the treatment of breast cancer, prostate cancer, multiple myeloma, melanoma, acute myeloid leukemia, glioblastoma, brain metastases, neurofibromatosis, gastrointestinal stromal tumors, rheumatoid arthritis, or multiple sclerosis.

[0470] In an eighty-fourth aspect, one or more compounds as described herein that are dual Fms/Flt-3 inhibitors can be used in the preparation of a medicament for the treatment of breast cancer, prostate cancer, multiple myeloma, melanoma, acute myeloid leukemia, glioblastoma, brain metastases, neurofibromatosis, gastrointestinal stromal tumors, rheumatoid arthritis, or multiple sclerosis, preferably wherein the disease is acute myeloid leukemia.

[0471] In an eighty-fifth aspect, one or more compounds as described herein that are dual Fms/Trk inhibitors can be used in the preparation of a medicament for the treatment of pancreatic cancer, prostate cancer, and multiple myeloma.

[0472] In an eighty-sixth aspect, there are provided compounds of Formula I for the treatment of a disease or condition related to Kit selected from the group consisting of malignancies, including, but not limited to, mast cell tumors, small cell lung cancer, non-small cell lung cancer (NSCLC), testicular cancer, pancreatic cancer, breast cancer, prostate cancer, merkel cell carcinoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, gastrointestinal stromal tumors (GISTs), multiple myeloma, tumor angiogenesis, brain metastases, glioblastoma, astrocytoma, neuroblastoma, neurofibromatosis (including Schwann cell neoplasia associated with neurofibromatosis), acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, mastocytosis, melanoma, and canine mast cell tumors; cardiovascular disease, including but not limited to atherosclerosis, cardiomyopathy, heart failure, pulmonary arterial hypertension and pulmonary fibrosis; inflammatory and autoimmune indications, including, but not limited to, allergy, anaphylaxis, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel disease, transplant rejection, hypereosinophilia, urticaria and dermatitis; gastrointestinal indications, including but not limited to gastroesophageal reflux disease (GERD), esophagitis, and gastrointestinal tract ulcers; ophthalmic indications, including but not limited to uveitis and retinitis; and neurologic indications, including but not limited to migraine.

[0473] In an eighty-seventh aspect there are provided compounds of Formula I for the treatment of a disease or condition related to Fms selected from the group consisting of inflammatory and autoimmune indications, including, but not limited to, rheumatoid arthritis, osteoarthritis, psoriatic arthritis, psoriasis, dermatitis, ankylosing spondylitis, polymyositis, dermatomyositis, systemic sclerosis, juvenile idiopathic arthritis, polymyalgia rheumatica, Sjogren's disease, Langerhan's cell histiocytosis (LCH), Still's disease, inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic lupus erythematosis (SLE), immune thrombocytopenic purpura (ITP), myelopreparation for autologous transplantation, transplant rejection, chronic obstructive pulmonary disease (COPD), emphysema, Kawasaki's Disease, hemophagocytic syndrome (macrophage activation syndrome), multicentric reticulohistiocytosis, and atherosclerosis; metabolic disorders, including, but not limited to, Type I diabetes, Type II diabetes, insulin resistance, hyperglycemia, obesity, and lipolysis;

disorders of bone structure, mineralization and bone formation and resorption, including, but not limited to, osteoporosis, osteodystrophy, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis (e.g. osteomyelitis), and peri-prosthetic or wear-debris-mediated osteolysis; kidney and genitourinary diseases, including, but not limited to, endometriosis, nephritis (e.g. glomerulonephritis, interstitial nephritis, Lupus nephritis), tubular necrosis, diabetes-associated renal complications (e.g. diabetic nephropathy), and renal hypertrophy; disorders of the nervous system, including, but not limited to, demyelinating disorders (e.g. multiple sclerosis, Charcot Marie Tooth syndrome), amyotrophic lateral sclerosis (ALS), myasthenia gravis, chronic demyelinating polyneuropathy, other demyelinating disorders, stroke, Alzheimer's disease and Parkinson's disease; pain, including, but not limited to, chronic pain, acute pain, inflammatory pain, neuropathic pain, bone pain; malignancies, including, but not limited to, multiple myeloma, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), lung cancer, pancreatic cancer, prostate cancer, breast cancer, ovarian cancer, neuroblastoma, sarcoma, osteosarcoma, giant cell tumors, (e.g. giant cell tumor of bone, giant cell tumor of tendon sheath (TGCT)), pigmented villonodular synovitis (PVNS), tumor angiogenesis, melanoma, glioblastoma multiforme, glioma, other tumors of the central nervous system, brain metasteses, osteolytic bone metastases, metastasis of tumors to other tissues, and other chronic myeloproliferative diseases such as myelofibrosis; vasculitis, including but not limited to collagen vascular disease, polyarteritis nodosa, Behcet's disease, sarcoidosis, familiar Mediterranean fever, Churg-Strauss vasculitis, temporal arteritis, giant cell arteritis, Takayasu's arteritis; ophthalmic indications, including but not limited to uveitis, scleritis, retinitis, age related macular degeneration, choroidal neovascularization, diabetic retinopathy; inherited disorders, including but not limited to cherubism, neurofibromatosis; infectious disease indications, including but not limited to infections associated with human immunodeficiency virus, hepatitis B virus, hepatitis C virus, human granulocytic anaplasmosis; lysosomal storage disorders, including but not limited to Gaucher's disease, Fabry's disease, Niemann-Pick disease; gastrointestinal indications, including but not limited to liver cirrhosis; pulmonary indications, including but not limited to pulmonary fibrosis, acute lung injury (e.g. ventilator-induced, smoke- or toxin-induced); global ischemia, and surgical indications, including but not limited to (cardiopulmonary) bypass surgery, vascular surgery, and vascular grafts.

[0474] In an eighty-eighth aspect, there are provided compounds of Formula I for the treatment of a disease or condition related to Flt-3 selected from the group consisting of malignancies, including, but not limited to, glioma, glioblastoma, brain metastases, lung cancer, breast cancer, colorectal cancer, prostate cancer, gastric cancer, esophageal cancer, pancreatic cancer, ovarian cancer, non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, acute lymphocytic leukemia, acute myeloid leukemia, acute myeloid leukemia with trilineage myelodysplasia, acute promyelocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, chronic neutrophilic leukemia, acute undifferentiated leukemia, anaplastic large-cell lymphoma, prolymphocyte leukemia, juvenile

myelomonocyctic leukemia, adult T-cell acute lymphocytic leukemia, T-cell type acute lymphocytic leukemia, B-cell type acute lymphocytic leukemia, mixed lineage leukemia, multiple myeloma, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myeloblastic leukemia, chronic myelomonocytic leukemia; other diseases including psoriasis, atopic dermatitis, axonal degeneration, acute transverse myelitis, amyotrophic lateral sclerosis, infantile spinal muscular atrophy, juvenile spinal muscular atrophy, Creutzfeldt- Jakob disease, subacute sclerosing panencephalitis, organ rejection, bone marrow transplant rejection, non-myeloablative bone marrow transplant rejection, ankylosing spondylitis, aplastic anemia, Behcet's disease, graft-versus-host disease, Graves' disease, autoimmune hemolytic anemia, Wegener's granulomatosis, hyper IgE syndrome, idiopathic thrombocytopenia purpura, Myasthenia gravis, type 1 diabetes mellitus, rheumatoid arthritis, Crohn's disease, multiple sclerosis, systemic lupus erythematosus, myelodysplastic syndrome, thrombocythemia, essential thrombocytosis, angiogenic myeloid metaplasia, myelofibrosis, myelofibrosis with myeloid metaplasia, chronic idiopathic myelofibrosis, polycythemia vera, anemia, leukopenia, neutropenia, thrombocytopenia, granulocytopenia, and pancytopenia.

[0475] In an eighty-ninth aspect, there are provided compounds of Formula I for the treatment of a disease or condition related to Trk selected from the group consisting of malignancies, including, but not limited to, prostate cancer, small cell lung cancer, non-small cell lung cancer, Wilms tumors, mesoblastic nephroma, infantile fibrosarcoma, neuroblastoma, brain cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, breast cancer, head and neck cancer, esophageal cancer, colorectal cancer, renal cancer, hepatocellular cancer, ovarian cancer, gynecological cancer, thyroid cancer, cervical cancer, ewings tumor, tumors of the central and peripheral nervous system, melanoma, multiple myeloma, acute myelogenous leukemia, and myeloid leukemia; neuropathies, including, but not limited to, stroke, multiple sclerosis, Parkinson's disease, Alzheimer's disease, transverse myelitis, and encephalitis; pain, including, but not limited to, chronic pain, acute pain, inflammatory pain, neuropathic pain, and pain associated with cancer, surgery, or bone fracture; bone-related diseases, including, but not limited to, metastatic bone disease, treatment-induced bone loss, osteoporosis, rheumatoid arthritis, ankylosing spondylitis, Paget's disease, and periodontal disease; other diseases, including, but not limited to, asthma, arthritis, diabetic retinopathy, macular degeneration, psoriasis, acute and chronic inflammation, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, fibrosarcoma, osteosarcoma, panic disorder, and infectious disease (e.g. Typanosoma cruzi infection (Chagas disease)).

[0476] In a ninetieth aspect, there are provided compounds of Formula I for the treatment of a disease or condition selected from the group consisting of rheumatoid arthiritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, systemic sclerosis, demyelinating disorders, multiple sclerosis, Charcot Marie Tooth syndrome, amyotrophic lateral sclerosis, Alzheimer's disease,

Parkinson's disease, global ischemia, ulcerative colitis, Crohn's disease, immune thrombocytopenic purpura, atherosclerosis, systemic lupus erythematosis, myelopreparation for autologous transplantation, transplant rejection, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, renal hypertrophy, type I diabetes, acute pain, inflammatory pain, neuropathic pain, acute myeloid leukemia, melanoma, multiple myeloma, breast cancer, prostate cancer, pancreatic cancer, lung cancer, ovarian cancer, gliomas, glioblastomas, neurofibromatosis, osteolytic bone metastases, brain metastases, gastrointestinal stromal tumors, and giant cell tumors.

[0477] In a ninety-first aspect, there are provided compounds of Formula I for the treatment of a disease or condition selected from the group consisting of rheumatoid arthiritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, multiple sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, renal hypertrophy, acute myeloid leukemia, melanoma, multiple myeloma, breast cancer, prostate cancer, pancreatic cancer, glioblastoma, neurofibromatosis, brain metastases, and gastrointestinal stromal tumors.

[0478] In a ninety-second aspect, there are provided compounds as described herein that are Kit inhibitors for the treatment of a disease or condition selected from the group consisting of rheumatoid arthritis, gastrointestinal stromal tumors, melanoma and neurofibromatosis.

[0479] In a ninety-third aspect, there are provided compounds as described herein that are Fms selective inhibitors for the treatment of a disease or condition selected from the group consisting of multiple sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, rheumatoid arthritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, glomerulonephritis, interstitial nephritis, Lupus nephritis, diabetic nephropathy, and renal hypertrophy.

[0480] In a ninety-fourth aspect, there are provided compounds as described herein that are Fms selective inhibitors that effectively cross the blood brain barrier for the treatment of a disease or condition selected from the group consisting of multiple sclerosis, glioblastoma, Alzheimer's disease, Parkinson's disease, and global ischemia.

[0481] In a ninety-fifth aspect, there are provided compounds as described herein that are Fms selective inhibitors that do not effectively cross the blood brain barrier for the treatment of a disease or condition selected from the group consisting of rheumatoid arthritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, glomerulonephritis, interstitial nephritis, Lupus nephritis, diabetic nephropathy, and renal hypertrophy.

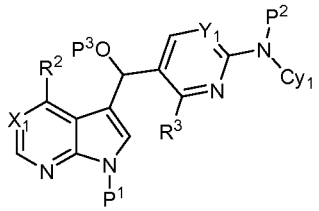
[0482] In a ninety-sixth aspect, there are provided compounds as described herein that are dual Fms/Kit inhibitors for the treatment of a disease or condition selected from the group consisting of breast cancer, prostate cancer, multiple myeloma, melanoma, acute myeloid leukemia, glioblastoma,

brain metastases, neurofibromatosis, gastrointestinal stromal tumors, rheumatoid arthritis, and multiple sclerosis.

[0483 In a ninety-seventh aspect, there are provided compounds as described herein that are dual Fms/Flt-3 inhibitors for the treatment of a disease or condition selected from the group consisting of breast cancer, prostate cancer, multiple myeloma, melanoma, acute myeloid leukemia, glioblastoma, brain metastases, neurofibromatosis, gastrointestinal stromal tumors, rheumatoid arthritis, and multiple sclerosis, preferably wherein the disease is acute myeloid leukemia.

[0484] In a ninety-eighth aspect, there are provided compounds as described herein that are dual Fms/Trk inhibitors for the treatment of a disease or condition selected from the group consisting of pancreatic cancer, prostate cancer, and multiple myeloma.

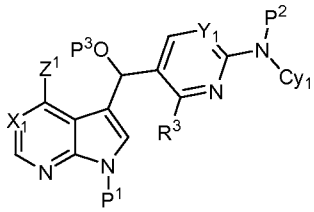
[0485] In a ninety-nineth aspect, the invention provide a compound of Formula II:



(II)

wherein P^1 and P^2 are each independently H or an amino protecting group. P^3 is H or a hydroxyl protecting group or a labile group. In one embodiment, P^1 and P^2 are each independently amino protecting group. In one embodiment, P^3 is H. All the other variables X_1, R^2, R^3, Y_1 and Cy_1 are as defined in any of the embodiments of Formula I described herein.

[0486] In a 100th aspect, the invention provides a compound of Formula IIa:



IIa

wherein P^1 and P^2 are each independently H or an amino protecting group. P^3 is H or a hydroxyl protecting group or a labile group. Z^1 is Br, Cl or R^2, wherein R^2 is as defined in any of the embodiments of formula I descried herein. In one embodiment, Z^1 is Cl or Br. In one embodiment, P^1 and P^2 are each independently amino protecting group. In one embodiment, P^3 is H. All the other variables X_1, R^3, Y_1 and Cy_1 are as defined in any of the embodiments of Formula I described herein.

[0487] In a 101st aspect, the invention provides a method of preparing a compound of Formula I. The method includes contacting a compound of Formula II with an agent under conditions sufficient

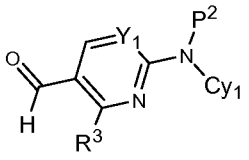
to form a compound of Formula I. The agent can be an oxidizing or a reducing agent. Exemples of the oxidizing agent include, but are not limited to, Dess-Martin periodinane (DMP). Examples of the reducing agents include, but are not limited to, trialkylsilane. In some embociments, the method is provided to prepare any of the compounds set forth in Tables 1 or 2, or any of compounds of Formula I or any compounds as described herein.

[0488] In a 102nd aspect, the invention provides a method of preparing a compound of Formulas II or IIa. The method includes contacting a compound of Formula III:



III

with a compound of Formula IV:



IV

under conditions sufficient to form a compound of Formula II or IIa, wherein Z^2 is Br, Cl or R^2 as defined in any of the embodiments described herein; Z^3 is iodo, a leaving group or a labile group; P^1 and P^2 are each independently an amino protecting group. In one embodiment, Z^2 is Cl or Br and Z^3 is I. In another embodiment, Z^2 is R^2. In some embodiments, Z^3 is iodo, methanesulfonyloxy, p-toluenesulfonyloxy, trifluoromethanesulfonyloxy. All the other variables X_1, R^3, Y_1 and Cy_1 are as defined in any of the embodiments of Formula I described herein. In some embociments, the method is provided to prepare any of the compounds set forth in Tables 1 or 2, or any of compounds of Formula I or any of the compounds as described herein. In some embodiments, a compound of Formula IV is an aldehyde selected from those set forth in Tables 3, 4, 5 and/or 6. In some embodiments, compounds of Formula III is a pyrrolo[2,3-b]pyridine compound selected from those set forth in Tables 4, 5 and/or 6. In some embodiments, compounds of formula IV is a pyrrolo[2,3-b]pyrimidine selected from those set forth in Table 5.

[0489] Any one or more of compounds of Formula I demonstrate desirable inhibitory activity on one or more of Fms, Kit, Flt3 and Trk kinases, including desirable activity profiles as described herein with selectivity relative to other kinases. Compounds of Formula I further demonstrate one or more desirable properties, including enhanced pharmacokinetic properties, favorable solubility, favorable lack of Cyp inhibition, and the like.

[0490] Additional aspects and embodiments will be apparent from the following Detailed Description of the Invention and from the claims.

DETAILED DESCRIPTION OF THE INVENTION

[0491] As used herein the following definitions apply unless clearly indicated otherwise:

[0492] It is noted here that as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

[0493] 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.

[0494] “Halogen” refer to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

[0495] "Haloalkyl," is meant to include alkyl substituted by one to seven halogen atoms. Haloalkyl includes monohaloalkyl and polyhaloalkyl. For example, the term "C_{1}-$_{6}$ haloalkyl" is meant to include trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0496] “Hydroxyl” or "hydroxy" refer to the group -OH.

[0497] “Thiol” refers to the group -SH.

[0498] “Lower alkyl” alone or in combination means an alkane-derived radical containing from 1 to 6 carbon atoms (unless otherwise specified) 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, 1-3, or 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like. In some instances, the option of the number of carbon atoms in a lower alkyl is specificied, for example, C_{1-3} alkyl refers to lower alkyl having 1, 2 or 3 carbon atoms. A "substituted lower alkyl" denotes lower alkyl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4, 5 or 6, also 1, 2, or 3 substituents, as described

herein, attached at any available atom to provide a stable compound. 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, 5 or 6 fluoro atoms, also 1, 2, or 3 fluoro atoms. It is understood that substitutions are chemically feasible and attached at any available atom to provide a stable compound.

[0499] "Lower alkoxy" denotes the group -OR^a, where R^a is lower alkyl. In some instances, the option of the number of carbon atoms in the lower alkyl is specificied, for example, C_{1-3} alkoxy refers to lower alkoxy having 1, 2 or 3 carbon atoms. "Substituted lower alkoxy" denotes lower alkoxy in which R^z is lower alkyl substituted with one or more substituents as indicated herein, for example, in the description of compounds of Formula I, including descriptions of substituted cycloalkyl, phenyl and heteroaryl, attached at any available atom to provide a stable compound. Preferably, substitution of lower alkoxy is with 1, 2, 3, 4, 5 or 6 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, 5 or 6 fluoro atoms, also 1, 2, or 3 fluoro atoms. It is understood that substitutions on alkoxy are chemically feasible and attached at any available atom to provide a stable compound.

[0500] "Lower alkylthio" denotes the group –SR^b, where R^b is lower alkyl. In some instances, the option of the number of carbon atoms in the lower alkyl is specificied, for example, C_{1-3} alkylthio refers to lower alkylthio having 1, 2 or 3 carbon atoms. "Substituted lower alkylthio" denotes lower alkylthio in which R^z is lower alkyl substituted with one or more substituents as indicated herein, for example, in the description of compounds of Formula I, including descriptions of substituted cycloalkyl, phenyl and heteroaryl, attached at any available atom to provide a stable compound. Preferably, substitution of lower alkylthio is with 1, 2, 3, 4, 5 or 6 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, 5 or 6 fluoro atoms, also 1, 2, or 3 fluoro atoms. It is understood that substitutions on alkylthio are chemically feasible and attached at any available atom to provide a stable compound.

[0501] "Lower alkylsulfonyl" denotes the group –$S(O)_2R^c$, where R^c is lower alkyl. In some instances, the option of the number of carbon atoms in the lower alkyl is specificied, for example, C_{1-3} alkylsulfonyl refers to lower alkylsulfonyl having 1, 2 or 3 carbon atoms. "Substituted lower alkylsulfonyl" denotes lower alkysulfonyl in which R^z is lower alkyl substituted with one or more substituents as indicated herein, for example, in the description of compounds of Formula I, including descriptions of substituted cycloalkyl, phenyl and heteroaryl, attached at any available atom to provide a stable compound. Preferably, substitution of lower alkylsulfonyl is with 1, 2, 3, 4, 5 or 6

substituents, also 1, 2, or 3 substituents. For example "fluoro substituted lower alkylsulfonyl" denotes lower alkylsulfonyl in which the lower alkyl is substituted with one or more fluoro atoms, where preferably the lower alkylsulfonyl is substituted with 1, 2, 3, 4, 5 or 6 fluoro atoms, also 1, 2, or 3 fluoro atoms. It is understood that substitutions on alkylsulfonyl are chemically feasible and attached at any available atom to provide a stable compound.

[0502] "Cycloalkyl" refers to saturated or unsaturated, non-aromatic monocyclic carbon ring systems of 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, and the like. In some instances, the option of the number of carbon atoms in the cycloalkyl is specificied, for example, C_{1-3} cycloalkyl refers to cycloalkyl having 1, 2 or 3 carbon atoms. 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, as described herein, attached at any available atom to provide a stable compound. It is understood that substitutions are chemically feasible and attached at any available atom to provide a stable compound.

[0503] "Cycloalkylalkyl" refers to an -(alkylene)-cycloalkyl group where alkylene as defined herein has the indicated number of carbon atoms or if unspecified having six or fewer, preferably four or fewer main chain carbon atoms; and cycloalkyl is as defined herein has the indicated number of carbon atoms. C_{3-8}cycloalkylalkyl is meant to have 3 to 8 ring carbon atoms. Exemplary cycloalkylalkyl include, e.g., cyclopropylmethylene, cyclobutylethylene, cyclobutylmethylene, and the like.

[0504] The term "alkylene" by itself or as part of another substituent means a linear or branched saturated divalent hydrocarbon moiety derived from an alkane having the number of carbon atoms indicated in the prefix. For example, (i.e., C_{1-6} means one to six carbons; C_{1-6} alkylene is meant to include methylene, ethylene, propylene, 2-methylpropylene, pentylene, hexylene and the like). C_{1-4} alkylene includes methylene $-CH_2-$, ethylene $-CH_2CH_2-$, propylene $-CH_2CH_2CH_2-$, and isopropylene $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-CH_2-(CH_2)_2CH_2-$, $-CH_2-CH(CH_3)CH_2-$, $-CH_2-C(CH_3)_2-$, $-CH_2-CH_2CH(CH_3)-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer, 8 or fewer, or 6 or fewer carbon atoms being preferred in the present invention. When a prefix is not included to indicate the number of carbon atoms in an alkylene portion, the alkylene moiety or portion thereof will have 12 or fewer main chain carbon atoms or 8 or fewer main chain carbon atoms, 6 or fewer main chain carbon atoms or 4 or fewer main chain carbon atoms.

[0505] "Aryl" by itself or as part of another substituent refers to a monocyclic, bicyclic or polycyclic polyunsaturated aromatic hydrocarbon moiety containing 6 to 14 ring carbon atoms. Non-limiting examples of unsubstituted aryl groups include phenyl, 1-naphthyl, 2-naphthyl and

4-biphenyl. Exemplary aryl group, such as phenyl or naphthyl, which may be optionally fused with a cycloalkyl of preferably 5-7, more preferably 5-6, ring members.

[0506] "Arylalkyl" refers to -(alkylene)-aryl, where the alkylene group is as defined herein and has the indicated number of carbon atoms, or if unspecified having six or fewer main chain carbon atoms or four or fewer main chain carbon atoms; and aryl is as defined herein. Examples of arylalkyl include benzyl, phenethyl, and the like.

[0507] A "substituted phenyl" is a phenyl ring that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, as described herein, attached at any available atom to provide a stable compound. It is understood that substitutions are chemically feasible and attached at any available atom to provide a stable compound.

[0508] "Heteroaryl" by itself or as part of another substituent refers to a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1-4, more preferably 1-3, even more preferably 1-2, heteroatoms independently selected from the group consisting of O, S, and N. "5 or 6 membered heteroaryl" alone or in combination refers to a monocyclic aromatic ring structure containing 5 or 6 ring 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, indolizinyl, benzo[b]thienyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, pyrazolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazolyl, furanyl, benzofuryl, indolyl, triazinyl, quinoxalinyl, cinnolinyl, phthalaziniyl, benzotriazinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiaxolyl, benzothienyl, quinolyl, isoquinolyl, indazolyl, pteridinyl and thiadiazolyl, and the like. 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, as described herein, attached at any available atom to provide a stable compound. It is understood that substitutions are chemically feasible and attached at any available atom to provide a stable compound.

[0509] "Heteroarylalkyl" refers to -(alkylene)-heteroaryl, where the alkylene group is as defined herein and has the indicated number of carbon atoms, or if unspecified having six or fewer main chain

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

[0510] "Heterocycloalkyl" refers to a saturated or unsaturated non-aromatic cycloalkyl group that contains from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized, the remaining ring atoms being C, where one or two C atoms may optionally be replaced by a carbonyl. The heterocycloalkyl may be a monocyclic, a bicyclic or a polycylic ring system of 3 to 12, preferably 4 to 10 ring atoms, more preferably 5 to 8 ring atoms in which one to five ring atoms are heteroatoms selected from –N=, -N-, -O-, -S-, -S(O)-, or $–S(O)_2$- and further wherein one or two ring atoms are optionally replaced by a -C(O)- group. The heterocycloalkyl can also be a heterocyclic alkyl ring fused with a cycloalkyl, an aryl or a heteroaryl ring. Non limiting examples of heterocycloalkyl groups include pyrrolidinyl, piperidinyl, imidazolidinyl, pyrazolidinyl, butyrolactam moiety, valerolactam moiety, imidazolidinone moiety, hydantoin, dioxolane moiety, phthalimide moiety, piperidine, 1,4-dioxane moiety, morpholinyl, thiomorpholinyl, thiomorpholinyl-S-oxide, thiomorpholinyl-S,S-oxide, piperazinyl, pyranyl, pyridine moiety, 3-pyrrolinyl, thiopyranyl, pyrone moiety, tetrahydrofuranyl, tetrahydrothiophenyl, quinuclidinyl, and the like. A heterocycloalkyl group can be attached to the remainder of the molecule through a ring carbon or a heteroatom.

[0511] "Heterocycloalkylalkyl" refers to -(alkylene)-heterocycloalkyl, where the alkylene group is as defined herein and has the indicated number of carbon atoms, or if unspecified having six or fewer main chain carbon atoms or four or fewer main chain carbon atoms; and heterocycloalkyl is as defined herein. Examples of heterocycloalkylalkyl include 2-pyridylmethyl, 2-thiazolylethyl, and the like.

[0512] "Protecting group" refers to a grouping of atoms that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity. Examples of protecting groups can be found in T.W. Greene and P.G. Wuts, PROTECTIVE GROUPS IN ORGANIC CHEMISTRY, (Wiley, 4th ed. 2006), Beaucage and Iyer, *Tetrahedron* 48:2223-2311 (1992), and Harrison and Harrison *et al.*, COMPENDIUM OF SYNTHETIC ORGANIC METHODS, Vols. 1-8 (John Wiley and Sons. 1971-1996). Representative amino protecting groups include formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (CBZ), *tert*-butoxycarbonyl (Boc), trimethyl silyl (TMS), 2-trimethylsilyl-ethanesulfonyl (SES), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (FMOC), nitro-veratryloxycarbonyl (NVOC), tri-isopropylsilyl (TIPS), phenylsulphonyl and the like (see also, Boyle, A. L. (Editor), carbamates, amides, N-sulfonyl derivatives, groups of formula -C(O)OR, wherein R is, for example, methyl, ethyl, t-butyl, benzyl, phenylethyl, CH_2=$CHCH_2$-, and the like, groups of the formula -C(O)R', wherein R' is, for example, methyl, phenyl, trifluoromethyl, and the like, groups of the formula -SO_2R", wherein R" is, for example, tolyl, phenyl, trifluoromethyl, 2,2,5,7,8-pentamethylchroman-6-yl, 2,3,6-trimethyl-4-

methoxyphenyl, and the like, and silanyl containing groups, such as 2-trimethylsilylethoxymethyl, t-butyldimethylsilyl, triisopropylsilyl, and the like, CURRENT PROTOCOLS IN NUCLEIC ACID CHEMISTRY, John Wiley and Sons, New York,Volume 1, 2000). Representative hydroxyl protecting groups include, but are not limited to, acetyl, benzoyl,dimethoxytrityl, methoxyethyoxymethyl, methoxymethyl, p-methoxybenzyl, tetrahydropyranyl, methylthiomethyl, trityl, t-butyldimethylsilyloxymethyl and trialkylsilyl, such as TMS, TIPS and the like.

[0513] As used herein, "Leaving group" or "Labile group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or a group capable of being displaced by a nucleophile and includes halo (such as chloro, bromo, and iodo), alkanesulfonyloxy, arenesulfonyloxy, alkylcarbonyloxy (e.g., acetoxy), arylcarbonyloxy, mesyloxy, tosyloxy, trifluoromethanesulfonyloxy, aryloxy (e.g., 2,4-dinitrophenoxy), methoxy, N,O-dimethylhydroxylamino, and the like.

[0514] "Tautomer" means compounds produced by the phenomenon wherein a proton of one atom of a molecule shifts to another atom. *See*, Jerry March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structures*, Fourth Edition, John Wiley & Sons, pages 69-74 (1992). The tautomers also refer to one of two or more structural isomers that exist in equilibrium and are readily converted from one isomeric form to another. Examples of include keto-enol tautomers, such as acetone/propen-2-ol, imine-enamine tautomers and the like, ring-chain tautomers, such as glucose/2,3,4,5,6-pentahydroxy-hexanal and the like, the tautomeric forms of heteroaryl groups containing a -N=C(H)-NH- ring atom arrangement, such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles. Where the compound contains, for example, a keto or oxime group or an aromatic moiety, tautomeric isomerism ('tautomerism') can occur. The compounds described herein may have one or more tautomers and therefore include various isomers. A person of ordinary skill in the art would recognize that other tautomeric ring atom arrangements are possible. All such isomeric forms of these compounds are expressly included in the present invention.

[0515] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. "Hydrate" refers to a complex formed by combination of water molecules with molecules or ions of the solute. "Solvate" refers to a complex formed by combination of solvent molecules with molecules or ions of the solute. The solvent can be an organic compound, an inorganic compound, or a mixture of both. Solvate is meant to include hydrate. Some examples of solvents include, but are not limited to, methanol, N,N-dimethylformamide, tetrahydrofuran, dimethylsulfoxide, and water. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are

equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention

[0516] As used herein, the term "Fms and Kit related disease or condition" refers to a disease or condition in which the biological function of a Fms protein kinase, including any mutation thereof, a Kit protein kinase, including any mutation thereof, or both a Fms and Kit protein kinase, including any mutations thereof, affects the development, course, and/or symptoms of the disease or condition, and/or in which modulation of the Fms and/or Kit protein kinase alters the development, course, and/or symptoms of the disease or condition. A Fms and/or Kit related disease or condition includes a disease or condition for which modulation provides a therapeutic benefit, e.g. wherein treatment with a Fms and/or Kit protein kinase inhibitor, preferably a dual Fms/Kit inhibitor, 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.

[0517] As used herein, the term "Fms related disease or condition" and the like refers to a disease or condition in which the biological function of a Fms protein kinase, including any mutations thereof, affects the development, course, and/or symptoms of the disease or condition, and/or in which modulation of the Fms protein kinase alters the development, course, and/or symptoms of the disease or condition. The Fms related disease or condition includes a disease or condition for which Fms inhibition provides a therapeutic benefit, e.g. wherein treatment with a Fms inhibitor, preferably a Fms selective inhibitor 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.

[0518] As used herein, the terms "Kit related disease or condition" and the like refers to a disease or condition in which the biological function of a Kit protein kinase, including any mutations thereof, affects the development, course, and/or symptoms of the disease or condition, and/or in which modulation of the Kit protein kinase alters the development, course, and/or symptoms of the disease or condition. The Kit related disease or condition includes a disease or condition for which Kit inhibition provides a therapeutic benefit, e.g. wherein treatment with a Kit inhibitor, 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.

[0519] As used herein, the term "dual Fms/Kit inhibitor" refers to a compound that inhibits both Fms and Kit protein kinases, 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 Fms 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 Kit kinase activity assay, wherein the activity is

approximately equipotent on each. Compounds are considered approximately equipotent if the ratio of IC_{50} for Kit kinase activity divided by the IC_{50} for Fms kinase activity is in the range of 20 to 0.05, also 10 to 0.1, also 5 to 0.2. Such compounds are effective in treating a disease or condition that is either or both of a Fms related and Kit related disease or condition. 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 Fms kinase (and/or Kit kinase) is >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 dual Fms/Kit inhibitor may be used to treat any Fms related disease or condition, the dual inihibition of Fms and Kit provides beneficial effects in treating certain diseases or conditions, including, but not limited to, breast cancer, prostate cancer, multiple myeloma, melanoma, acute myeloid leukemia, glioblastoma, brain metastases, neurofibromatosis, gastrointestinal stromal tumors, rheumatoid arthritis, or multiple sclerosis.

[0520] As used herein, the term "dual Fms/Flt-3 inhibitor" refers to a compound that inhibits both Fms and Flt-3 protein kinases, 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 Fms 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 Flt-3 kinase activity assay, wherein the activity is approximately equipotent on each. Compounds are considered approximately equipotent if the ratio of IC_{50} for Flt-3 kinase activity divided by the IC_{50} for Fms kinase activity is in the range of 20 to 0.05, also 10 to 0.1, also 5 to 0.2. Such compounds are effective in treating a disease or condition that is either or both of a Fms related and Flt-3 related disease or condition. 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 Fms kinase (and/or Flt3 kinase) is >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 dual Fms/Flt-3 inhibitor may be used to treat any Fms related mediated disease or condition, the dual inihibition of Fms and Flt-3 provides beneficial effects in treating certain diseases or conditions, including, but not limited to, breast cancer, prostate cancer, multiple myeloma, melanoma, acute myeloid leukemia, glioblastoma, brain metastases, neurofibromatosis, gastrointestinal stromal tumors, rheumatoid arthritis, or multiple sclerosis.

[0521] As used herein, the term "dual Fms/Trk inhibitor" refers to a compound that inhibits both Fms and Trk protein kinases, 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 Fms 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 Trk kinase activity assay (i.e. any one or more of TrkA, TrkB and TrkC), wherein the activity is approximately equipotent on each. Compounds are considered approximately equipotent if the ratio of IC_{50} for Trk kinase activity (i.e. at least one of TrkA, TrkB and TrkC) divided by the IC_{50} for Fms kinase activity is in the range of 20 to 0.05, also 10 to 0.1, also 5 to 0.2. Such compounds are effective in treating a disease or condition that is either or both of a Fms related and Trk related disease or condition. 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 Fms kinase (and/or Trk kinase) is >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 dual Fms/Trk inhibitor may be used to treat any Fms related mediated disease or condition, the dual inihibition of Fms and Trk provides beneficial effects in treating certain diseases or conditions, including, but not limited to, pancreatic cancer, prostate cancer, and multiple myeloma.

[0522] As used herein, the term "Fms selective inhibitor" refers to a compound that selectively inhibits Fms kinase relative to Kit 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 Fms kinase activity assay and when determined in a comparable generally accepted Kit kinase activity assay will have a ratio of IC_{50} for Kit kinase divided by the IC_{50} for Fms kinase of >20, also >30, also >40, also >50, also >60, also >70, also >80, also >90, also >100. Such compounds are effective in treating a disease or condition that is Fms protein kinase mediated, without effecting Kit protein kinase. 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 Fms kinase is >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 Fms selective inhibitor may be used to treat any Fms related disease or condition, the Fms selectivity provides beneficial effects in treating certain diseases or conditions, including, but not limited to, multiple sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, rheumatoid arthritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, glomerulonephritis, interstitial nephritis, Lupus nephritis, diabetic nephropathy, or renal hypertrophy.

[0523] As used herein, the term "blood brain barrier" refers to the physical barrier in the circulation system that prevents many substances, including certain small molecule drugs, from entering into the central nervous system (CNS). Drugs which are intended to interact with molecular targets in the CNS must cross the blood brain barrier to reach their intended targets. Conversely, peripherally acting agents should not cross the blood brain barrier so as to avoid any CNS related side effects. The ability of a compound to penetrate the blood brain barrier is expressed as the blood brain barrier permeability or the ratio of the steady-state concentrations of the compound in the brain and in the blood. The experimental blood brain barrier permeability can be measured by *in vivo* methods. Various methods can be employed for measuring the fraction of compound transported from the blood to brain tissue, including brain blood partitioning, brain perfusion, brain uptake index, and intracerebral microdialysis. However, these *in vivo* methods are laborious and low-throughput in nature. In practice, *in silico* computational methods are often used to predict the blood brain barrier permeability prior to *in vivo* confirmation. Most of the blood brain barrier models that have been built so far are based on the assumption that the majority of the compounds are transported across the blood brain barrier by passive diffusion. Of all the physicochemical properties, polar surface area (PSA) shows the best correlation with the blood brain barrier permeability for passively diffused compounds. Empirical evidence suggests that compounds having a polar surface area of 100 or greater typically have a low probability of crossing the blood brain barrier. Polar surface area is readily calculated from the compound structure using a published algorithm (Ertl et al., J. Med. Chem. 2000, 43:3714-3717). While it is understood that a Fms selective inhibitor may be used to treat any Fms related disease or condition, compounds that effectively cross the blood brain barrier provide beneficial effects in treating certain diseases or conditions, including, but not limited to, multiple sclerosis, Alzheimer's disease, Parkinson's disease, and global ischemia, while compounds that do not effectively cross the blood brain barrier provide beneficial effects in treating certain diseases or conditions, including, but not limited to, rheumatoid arthritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, glomerulonephritis, interstitial nephritis, Lupus nephritis, diabetic nephropathy, or renal hypertrophy.

[0524] 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.

[0525] 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.

[0526] 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.

[0527] 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.

[0528] 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.

[0529] 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).

[0530] As used herein, the term "stoichiometry" refers to the molar ratio of two or more reactants that combine to form a complex, 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.

[0531] As used herein, the term "composition" refers to a pharmaceutical preparation suitable for administration to an intended animal 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.

[0532] 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.

[0533] 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.

[0534] "Unit dosage form" refers to a composition intended for a single administration to treat a subject suffering from a disease or medical condition. Each unit dosage form typically comprises each of the active ingredients of this invention plus pharmaceutically acceptable excipients. Examples of unit dosage forms are individual tablets, individual capsules, bulk powders, liquid solutions, ointments, creams, eye drops, suppositories, emulsions or suspensions. Treatment of the disease or

condition may require periodic administration of unit dosage forms, for example: one unit dosage form two or more times a day, one with each meal, one every four hours or other interval, or only one per day. The expression "oral unit dosage form" indicates a unit dosage form designed to be taken orally.

[0535] 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.

[0536] In the context of compounds binding to a target, the terms “greater affinity” and "selective" indicates that the compound binds more tightly than a reference compound, or than the same compound in a reference condition, *i.e.*, with a lower dissociation constant. In some embodiments, the greater affinity is at least 2, 3, 4, 5, 8, 10, 50, 100, 200, 400, 500, 1000, or 10,000-fold greater affinity.

[0537] As used herein in connection with compounds of the invention, the term “synthesizing” and like terms means chemical synthesis from one or more precursor materials.

[0538] By “assaying” is meant the creation of experimental conditions and the gathering of data regarding a particular result of the experimental conditions. For example, enzymes can be assayed based on their ability to act upon a detectable substrate. A compound or ligand can be assayed based on its ability to bind to a particular target molecule or molecules.

[0539] As used herein, the term “modulating” or “modulate” refers to an effect of altering a biological activity, especially a biological activity associated with a particular biomolecule such as a protein kinase. For example, an agonist or antagonist of a particular biomolecule modulates the activity of that biomolecule, *e.g.*, an enzyme, by either increasing (e.g. agonist, activator), or decreasing (e.g. antagonist, inhibitor) the activity of the biomolecule, such as an enzyme. Such activity is typically indicated in terms of an inhibitory concentration (IC_{50}) or excitation concentration (EC_{50}) of the compound for an inhibitor or activator, respectively, with respect to, for example, an enzyme.

[0540] 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.

[0541] "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, gall bladder, 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

[0542] 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 with respect to such kinase targets, as well as the following:

[0543] **Fms:** Target kinase Fms (i.e., feline McDonough sarcoma) is a member of the family of genes originally isolated from the Susan McDonough strain of feline sarcoma viruses. Fms is a transmembrane tyrosine kinase of 108.0 kDa coded by chromosome 5q33.2-q33.3 (symbol: CSF1R). The structure of the transmembrane receptor Fms comprises two Ig-like domains, a IgC2-like domain, two additional Ig-like domains, a TM domain, and the TK domain.

[0544] Fms is the receptor for the macrophage colony-stimulating factor (M-CSF), and is crucial for the growth and differentiation of the monocyte-macrophage lineage. Upon binding of M-CSF to the extracellular domain of Fms, the receptor dimerizes and trans-autophosphorylates cytoplasmic tyrosine residues.

[0545] M-CSF, first described by Robinson and co-workers (Blood. 1969, 33:396-9), is a cytokine that controls the production, differentiation, and function of macrophages. M-CSF stimulates differentiation of progenitor cells to mature monocytes, and prolongs the survival of monocytes. Furthermore, M-CSF enhances cytotoxicity, superoxide production, phagocytosis, chemotaxis, and secondary cytokine production of additional factors in monocytes and macrophages. Examples of such additional factors include granulocyte colony stimulating factor (G-CSF), interleukin-6 (IL-6), and interleukin-8 (IL-8). M-CSF stimulates hematopoiesis, promotes differentiation and proliferation of osteoclast progenitor cells, and has profound effects on lipid metabolism. Furthermore, M-CSF is important in pregnancy. Physiologically, large amounts of M-CSF are produced in the placenta, and M-CSF is believed to play an essential role in trophoblast differentiation (Motoyoshi, Int J Hematol. 1998, 67:109-22). The elevated serum M-CSF levels of early pregnancy may participate in the immunologic mechanisms responsible for the maintenance of the pregnancy (Flanagan & Lader, Curr Opin Hematol. 1998, 5:181-5).

[0546] Aberrant expression and/or activation of Fms has been implicated in acute myeloid leukemia, AML (Ridge et al, Proc. Nat. Acad. Sci., 1990, 87:1377-1380). Mutations at codon 301 are believed to lead to neoplastic transformation by ligand independence and constitutive tyrosine kinase activity of the receptor. The tyrosine residue at codon 969 has been shown to be involved in a negative regulatory activity, which is disrupted by amino acid substitutions. Accordingly, Fms mutations are most prevalent (20%) in chronic myelomonocytic leukemia and AML type M4 (23%), both of which are characterized by monocytic differentiation.

[0547] A condition related to AML is chronic myeloid leukemia (CML). During the myeloid blast crisis (BC) of CML, non-random additional chromosome abnormalities occur in over 80% of patients.

However, these cytogenetic changes have been reported to precede the clinical signs of CML-BC by several months to years suggesting that other biological events may participate in the multistep process of acute transformation of CML. The autocrine production of growth factors has been shown to occur in several hematological malignancies and particularly in AML. Specchia et al [Br J Haematol. 1992 Mar; 80(3):310-6] have demonstrated that IL-1 beta gene is expressed in almost all cases of CML in myeloid blast crisis, and that a high proportion of cases showed constitutive expression of the M-CSF gene. Many of the same patients in the Specchia et al study demonstrated simultaneous co-expression of Fms. After exposure of leukemic cells to phorbol myristate acetate (PMA), release of M-CSF protein was documented in three of five patients studied; however, no significant interleukin-3 (IL-3), granulocyte-macrophage colony-stimulating factor (GM-CSF) or granulocyte colony-stimulating factor (G-CSF), was detected in these patients. This demonstrates that different patterns of growth factors secretion exist in AML and CML, and that distinct molecular events are likely involved in the control of leukemic proliferation.

[0548] The observation that production of M-CSF, the major macrophage growth factor, is increased in tissues during inflammation (Le Meur et al, J. Leukocyte Biology. 2002;72:530-537) provides a role for Fms in certain diseases. For example, COPD is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The chronic inflammation of COPD is observed through the airways, parenchyma, and pulmonary vasculature. The inflammatory cell population consists of neutrophils, macrophages, and T lymphocytes, along with eosinophils in some patients. Macrophages are postulated to play an orchestrating role in COPD inflammation by releasing mediators such as TNF-a, IL-8 and LTB4, which are capable of damaging lung structures and/or sustaining neutrophilic inflammation.

[0549] Further, M-CSF/fms signaling is critical to osteoclast formation and survival of osteoclast precursors. For example, estrogen loss in menopause results in increased M-CSF and thus increased osteoclast number and bone resorption which leads to increased risk of fracture and osteoporosis. Accordingly, blockage of this signal is a target for the inhibition of bone resorption (Teitelbaum, Science. 2000;289:1504; Rohan, Science. 2000;289:1508).

[0550] Atherosclerosis, an inflammatory disease of the vessel walls, is associated with significant morbidity and mortality. A beneficial effect for Fms inhibition in the treatment and prevention of atherosclerosis depends on several observations (Libby, Nature. 2002;420:868-874). First, monocytes resident in the arterial intima increase expression of scavenger receptors and internalize modified lipoproteins. The resulting lipid-laden macrophages develop into foam cells characteristic of the atherosclerotic lesion. Macrophages in atheroma secrete cytokines and growth factors involved in lesion progression. Additionally, macrophages replicate within the intima. Through Fms, M-CSF

activates the transition from monocyte to lipid-laden macrophage and augments expression of scavenger receptor A. Indeed, atherosclerotic plaques over-express M-CSF which is critical for atherosclerotic progression. Mice deficient in M-CSF have been found to experience less severe atherosclerosis than mice with normal M-CSF (Rajavashisth, et. al., J. Clin. Invest. 1998;101:2702-2710; Qiao, et. al., Am. J. Path. 1997;150:1687-1699). Accordingly, inhibitors of Fms disrupt M-CSF signaling, compromising monocyte to macrophage foam cell progression, macrophage survival and replication, and cytokine signaling that participates in lesion progression.

[0551] The role of M-CSF and Fms in emphysema appears to involve the regulation of elastin metabolism through control of matrix metalloproteins. M-CSF has a role in the modulation of the accumulation and function of alveolar macrophages (AMs) in vivo (Shibata et al, Blood 2001, 98: pp. 2845-2852). Osteopetrotic (Op/Op) mice have no detectable M-CSF and show variable tissue-specific reductions in macrophage numbers. Accordingly, it was hypothesized that AMs would be decreased in number and have altered function in Op/Op mice because of the absence of M-CSF. Shibata et al found that lung macrophages identified in lung sections were decreased in number in 20-day-old Op/Op mice but not Op/Op mice older than 4 months compared with findings in age-matched littermate controls. The numbers of AMs recovered by bronchoalveolar lavage (BAL) were also reduced in young but not adult Op/Op mice compared with controls. Importantly, AMs of Op/Op mice spontaneously release higher levels of matrix metalloproteinases (MMPs) than AMs of controls. Consistent with an increased release of MMP, Op/Op mice have abnormal elastin deposition and spontaneously develop emphysema in the absence of molecular or cellular evidence of lung inflammation. Accordingly, the modulation of metalloelastase activity in macrophages by M-CSF may control the degradation of elastin fibers in lungs or blood vessels.

[0552] Metastatic cancer cells cause bone destruction, with associated fracture, pain, deformation, and hypercalcaemia, due to production of osteoclasticogenic factors including M-CSF by tumor cells (Clohisy et al, Clin. Orthop. 2000, 373: 104-14). Binding of M-CSF to the Fms product stimulates formation of osteoclasts and osteolytic activity (Kodama et al, J. Exp. Med. 1991, 173: 269-72; Feng et al, Endocrinology 2002, 143: 4868-74). Accordingly, inhibition of osteoclast activity at the level of Fms offers a compelling target for amelioration of bone metastasis.

[0553] Nephritis is inflammation of the kidneys. It may be caused for example by a bacterial infection of the kidneys or exposure to a toxin. However, nephritis more commonly develops from an abnormal immune reaction, which can occur, for example, when an antibody attacks either the kidney itself or an antigen attached to kidney cells, or when an antigen-antibody complex formed elsewhere in the body attachs to cells in the kidney. Some types of nephritis involve infiltration of kidney tissues by white blood cells and deposits of antibodies. In other types of nephritis, inflammation may consist of tissue swelling or scarring without white blood cells or antibodies. Furthermore, nephritis

can occur anywhere in the kidneys. With respect to the glomeruli, progressive damage to glomeruli causes urine production to fall and metabolic waste products to build up in the blood. When damage to glomeruli is severe, inflammatory cells and injured glomerular cells accumulate, compressing the capillaries within the glomerulus and interfering with filtration. Scarring may develop, impairing kidney function and reducing urine production. In some cases, microthrombi may form in the small blood vessels, further decreasing kidney function. Less commonly, nephritis involves the tubulointerstitial tissues; such inflammation is called tubulointerstitial nephritis. When inflammation damages the tubules and the tubulointerstitial tissues, the kidneys may become unable to concentrate urine, eliminate (excrete) metabolic waste products from the body, or balance the excretion of sodium and other electrolytes, such as potassium. When the tubules and tubulointerstitial tissues are damaged, kidney failure often develops. Accordingly, inhibition of Fms offers a target for therapeutic intervention in nephritis due to the modulation of the inflammatory response comprising the etiology of the disease.

[0554] Lupus nephritis, i.e., renal involvement in systemic lupus erythematosus (SLE), is a common disease manifestation with a poor prognosis. At least three potentially overlapping, immuno-pathogenic mechanisms for lupus nephritis are supported by experimental data. First, circulating immune complexes consisting chiefly of DNA and anti-DNA are deposited in the kidney. Resulting complement activation and chemotaxis of neutrophils leads to a local inflammatory process. Second, in situ formation of antigen and antibody complexes may similarly lead to complement activation and leucocyte mediated injury. Third, antibodies against specific cellular targets may produce renal injury. An additional mechanism is observed in SLE patients with the antiphospholipid antibody syndrome. Glomerular thrombosis can result from the hypercoagulability that accompanies antibodies directed against negatively charged phospholipid-protein complexes (e.g. biologic false positive VDRL, anticardiolipin antibodies, and lupus anticoagulant). Mesangial lupus nephritis is accompanied by normal diagnostic findings or with a mild degree of proteinuria but typically absence of hypertension or abnormal urinary sediment. Focal and diffuse proliferative lupus glomerulonephritis are often associated with the worst prognosis for renal survival and can be accompanied by nephrotic syndrome, significant hypertension and abnormal urine sediment. Membranous lupus nephritis often presents with proteinuria, moderate to high grade, but usually normal urinary sediment in the absence of hypertension. Mesangial lupus nephropathy is generally associated with an excellent prognosis, whereas proliferative lupus nephropathy, especially diffuse variant, is often characterized by hypertension, red cell casts and significant deterioration of renal function. Nephrotic syndrome in the absence of hypertension, active urinary sediment or significant hypocomplementemia suggest the membranous variant of lupus nephropathy. Membranous nephropathy generally is associated with a good prognosis and relative preservation of renal function. However, in the presence of persistent nephrotic range proteinuria, membranous lupus nephropathy

can, in fact, lead to loss of renal function and end stage renal disease (ESRD). Accordingly, inhibition of Fms offers a target for therapeutic intervention in lupus due to the modulation of the inflammatory response comprising the etiology of the disease.

[0555] Macrophage accumulation is a prominent feature in many forms of glomerulonephritis. Local proliferation of macrophages within the kidney has been described in human and experimental glomerulonephritis and may have an important role in augmenting the inflammatory response. Isbel et al (Nephrol Dial Transplant 2001, 16: 1638-1647) examined the relationship between local macrophage proliferation and renal expression of M-CSF. Glomerular and tubulointerstitial M-CSF expression was found to be up-regulated in human glomerulonephritis, being most prominent in proliferative forms of disease. Because this correlates with local macrophage proliferation, it suggests that increased renal M-CSF production plays an important role in regulating local macrophage proliferation in human glomerulonephritis. In a model of renal inflammation (UUO- unilateral ureteric obstruction) anti-Fms antibody treatment reduced macrophage accumulation (Le Meur et.al., J Leukocyte Biology, 2002, 72: 530-537). Accordingly, inhibition of Fms offers a target for therapeutic intervention in glomerulonephritis.

[0556] Insulin resistance and obesity are hallmarks of type II diabetes and a strong correlation exists between insulin resistance and abdominal visceral fat accumulation (Bjorntrop, Diabetes Metab. Res. Rev., 1999, 15: 427-441). Current evidence indicates that macrophages accumulating in adipose tissue release TNF-a and other factors that cause adipocyte changes (hypertrophy, lipolysis, reduced insulin sensitivity) and also promote insulin resistance in surrounding tissues. Therefore, macrophage accumulation in type 2 diabetes is important for disease progression. Accordingly, inhibition of Fms has potential in preventing the development of insulin resistance and hyperglycemia.

[0557] Similarly, the observation that production of M-CSF, the major macrophage growth factor, is increased in tissues during inflammation points out a role for Fms in diseases, such as for example inflammatory diseases. More particularly, because elevated levels of M-CSF are found in the disease state, modulation of the activity of Fms can ameliorate disease associated with increased levels of M-CSF.

[0558] Fms inhibitors may be useful in treating inflammatory and autoimmune indications, including, but not limited to, rheumatoid arthritis, osteoarthritis, psoriatic arthritis, psoriasis, dermatitis, ankylosing spondylitis, polymyositis, dermatomyositis, systemic sclerosis, juvenile idiopathic arthritis, polymyalgia rheumatica, Sjogren's disease, Langerhan's cell histiocytosis (LCH), Still's disease, inflammatory bowel syndrome, ulcerative colitis, Crohn's disease, systemic lupus erythematosis (SLE), transplant rejection, chronic obstructive pulmonary disease (COPD), emphysema, Kawasaki's Disease, hemophagocytic syndrome (macrophage activation syndrome),

multicentric reticulohistiocytosis, and atherosclerosis; metabolic disorders, including, but not limited to, Type I diabetes, Type II diabetes, insulin resistance, hyperglycemia, obesity, and lipolysis; disorders of bone structure, mineralization and bone formation and resorption, including, but not limited to, osteoporosis, osteodystrophy, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis (e.g. osteomyelitis), and peri-prosthetic or wear-debris-mediated osteolysis; kidney and genitourinary diseases, including, but not limited to, endometriosis, nephritis (e.g. glomerulonephritis, interstitial nephritis, Lupus nephritis), tubular necrosis, diabetes-associated renal complications (e.g. diabetic nephropathy), and renal hypertrophy; disorders of the central nervous system, including, but not limited to, multiple sclerosis, amyotrophic lateral sclerosis (ALS), myasthenia gravis, chronic demyelinating polyneuropathy, other demyelinating disorders, stroke, Alzheimer's disease and Parkinson's disease; inflammatory and chronic pain, including, but not limited to, bone pain; malignancies, including, but not limited to, multiple myeloma, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), lung cancer, pancreatic cancer, prostate cancer, breast cancer, ovarian cancer, neuroblastoma, sarcoma, osteosarcoma, giant cell tumor of bone, giant cell tumor of tendon sheath (TGCT), pigmented villonodular synovitis (PVNS), tumor angiogenesis, melanoma, glioblastoma multiforme, glioma, other tumors of the central nervous system, metastasis of tumors to other tissues, and other chronic myeloproliferative diseases such as myelofibrosis; vasculitis, including but not limited to collagen vascular disease, polyarteritis nodosa, Behcet's disease, sarcoidosis, familiar Mediterranean fever, Churg-Strauss vasculitis, temporal arteritis, giant cell arteritis, Takayasu's arteritis; ophthalmic indications, including but not limited to uveitis, scleritis, retinitis, age related macular degeneration, choroidal neovascularization, diabetic retinopathy; inherited disorders, including but not limited to cherubism, neurofibromatosis; infectious disease indications, including but not limited to infections associated with human immunodeficiency virus, hepatitis B virus, hepatitis C virus, human granulocytic anaplasmosis; lysosomal storage disorders, including but not limited to Gaucher's disease, Fabry's disease, Niemann-Pick disease; gastrointestinal indications, including but not limited to liver cirrhosis; pulmonary indications, including but not limited to pulmonary fibrosis, acute lung injury (e.g. ventilator-induced, smoke- or toxin-induced); and surgical indications, including but not limited to (cardiopulmonary) bypass surgery, vascular surgery, and vascular grafts.

[0559] **Kit:** Target kinase Kit (i.e., feline Hardy-Zuckerman 4 sarcoma viral oncogene) is a 109.9 kDa transmembrane tyrosine kinase encoded by chromosome 4q12 (symbol: KIT). Receptor protein tyrosine kinases (RPTKs) regulate key signal transduction cascades that control cellular growth and proliferation. The Stem Cell Factor (SCF) receptor Kit is a type III transmembrane RPTK that includes five extracellular immunoglobulin (IG) domains, a single transmembrane domain, and a split cytoplasmic kinase domain separated by a kinase insert segment. Kit plays an important role in the development of melanocytes, mast, germ, and hematopoietic cells.

[0560] Stem Cell Factor (SCF) is a protein encoded by the S1 locus, and has also been called kit ligand (KL) and mast cell growth factor (MGF), based on the biological properties used to identify it (reviewed in Tsujimura, Pathol Int 1996, 46:933-938; Loveland, et al., J. Endocrinol 1997, 153:337-344; Vliagoftis, et al., Clin Immunol 1997, 100:435-440; Broudy, Blood 1997, 90:1345-1364; Pignon, Hermatol Cell Ther 1997, 39:114-116; and Lyman, et al., Blood 1998, 91:1101-1134.). Herein the abbreviation SCF refers to the ligand for Kit.

[0561] SCF is synthesized as a transmembrane protein with a molecular weight of 220 or 248 Dalton, depending on alternative splicing of the mRNA to encode exon 6. The larger protein can be proteolytically cleaved to form a soluble, glycosylated protein which noncovalently dimerizes. Both the soluble and membrane-bound forms of SCF can bind to and activate Kit. For example, in the skin, SCF is predominantly expressed by fibroblasts, keratinocytes, and endothelial cells, which modulate the activity of melanocytes and mast cells expressing Kit. In bone, marrow stromal cells express SCF and regulate hematopoiesis of Kit expressing stem cells. In the gastrointestinal tract, intestinal epithelial cells express SCF and affect the interstitial cells of Cajal and intraepithelial lymphocytes. In the testis, sertoli cells and granulosa cells express SCF which regulates spermatogenesis by interaction with Kit on germ cells.

[0562] According to OMIM, signaling from Kit is essential for primordial germ cell growth both in vivo and in vitro. Many downstream effectors of the KIT signaling pathway have been identified in other cell types, but how these molecules control primordial germ cell survival and proliferation are unknown. Determination of the KIT effectors acting in primordial germ cells has been hampered by the lack of effective methods to manipulate easily gene expression in these cells. De Miguel et al. (2002) overcame this problem by testing the efficacy of retroviral-mediated gene transfer for manipulating gene expression in mammalian germ cells. They found that primordial germ cells can successfully be infected with a variety of types of retroviruses. They used this method to demonstrate an important role of the AKT1 in regulating primordial germ cell growth (OMIM MIM Number: 164920: 04/17/2006).

[0563] Aberrant expression and/or activation of Kit has been implicated in a variety of pathologic states. For example, evidence for a contribution of Kit to neoplastic pathology includes its association with leukemias and mast cell tumors, small cell lung cancer, testicular cancer, and some cancers of the gastrointestinal tract and central nervous system. In addition, Kit has been implicated in playing a role in carcinogenesis of the female genital tract sarcomas of neuroectodermal origin, and Schwann cell neoplasia associated with neurofibromatosis. It was found that mast cells are involved in modifying the tumor microenvironment and enhancing tumor growth (Yang et al., J Clin Invest. 2003, 112:1851-1861; Viskochil, J Clin Invest. 2003, 112:1791-1793).

[0564] Kit inhibitors may be useful in treating malignancies, including, but not limited to, mast cell tumors, small cell lung cancer, non-small cell lung cancer (NSCLC), testicular cancer, pancreatic cancer, breast cancer, merkel cell carcinoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, gastrointestinal stromal tumors (GISTs), tumor angiogenesis, glioblastoma, astrocytoma, neuroblastoma, Schwann cell neoplasia associated with neurofibromatosis, neurofibromatosis not associated with Schwann cell neoplasia, acute myelocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, mastocytosis, melanoma, and canine mast cell tumors; cardiovascular disease, including but not limited to atherosclerosis, cardiomyopathy, heart failure, pulmonary hypertension; inflammatory and autoimmune indications, including, but not limited to, allergy, anaphylaxis, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, hypereosinophilia, urticaria and dermatitis; gastrointestinal indications, including but not limited to gastroesophageal reflux disease (GERD), esophagitis, and gastrointestinal tract ulcers; ophthalmic indications, including but not limited to uveitis and retinitis; and neurologic indications, including but not limited to migraine.

[0565] **Flt3:** Target kinase Flt3 (i.e., Fms-like tyrosine kinase 3) is a transmembrane tyrosine kinase of 112.8 kDa encoded by chromosome 13q12 (symbol: FLT3). According to OMIM, Rosnet et al. (Genomics 1991, 9: 380-385) isolated a novel member of the class 3 receptors discussed above. They demonstrated that this gene of the tyrosine kinase family, called FLT3, has strong sequence similarities with other members of the group. Lymphohematopoietic stem cells serve as a reservoir for virtually all blood cells but make up only approximately 0.01% of human or murine marrow cells. The ability to isolate and expand this population has clinical applications in bone marrow transplantations for cancer and genetic diseases. Small et al. (Proc. Nat. Acad. Sci. 1994, 91: 459-463) cloned the cDNA for stem cell tyrosine kinase 1, the human homolog of murine Flk2/Flt3, from a CD34+ hematopoietic stem cell-enriched library. The cDNA encoded a protein of 993 amino acids with 85% identity and 92% similarity to the murine homolog. STK1, which is identical to FLT3, is a member of the type III receptor tyrosine kinase family that includes KIT, FMS, and platelet-derived growth factor receptor. STK1 expression in human blood and marrow is restricted to CD34+ cells, a population greatly enriched by stem/progenitor cells. Antisense oligonucleotides directed against STK1 sequences inhibited hematopoietic colony formation, most strongly in long-term bone marrow cultures. The data suggested that STK1 may function as a growth factor receptor on hematopoietic stem and/or progenitor cells (OMIM MIM Number: 136351: 03/03/2005).

[0566] Levis et al., state that Internal tandem duplication (ITD) mutations of the receptor tyrosine kinase FLT3 have been found in 20% to 30% of patients with acute myeloid leukemia (AML). These mutations constitutively activate the receptor and appear to be associated with a poor prognosis. In

their study, dose-response cytotoxic assays were performed with AG1295, a tyrosine kinase inhibitor active against FLT3, on primary blasts from patients with AML, and they found that AG1295 was specifically cytotoxic to AML blasts harboring FLT3/ITD mutations. They suggest that these mutations contribute to the leukemic process and that the FLT3 receptor represents a therapeutic target in AML (Levis et al., Blood 2001, 98:885-887). An Flt3 inhibitor may be useful in treating acute myeloid leukemia, myelodysplastic syndrome, acute lymphoblastic leukemia.

[0567] **TrkA:** Target kinase TrkA (i.e., neurotrophic tyrosine kinase, receptor, type 1) is a 140 kDa tyrosine kinase encoded by chromosome 1q21-q22 (symbol: NTRK1). TrkA inhibitors may be useful in treating pain (e.g. chronic pain, neuropathic pain), cancer (e.g. prostate cancer, lung cancer, myeloid leukemia, pancreatic cancer), allergic disorders (e.g. asthma), arthritis, diabetic retinopathy, macular degeneration and psoriasis.

[0568] TrkA is a plasma member receptor composed of an extracellular domain (responsible for high affinity binding to nerve growth factor, NGF), a transmembrane segment and an intracellular protein tyrosine kinase domain (responsible to transmit the NGF signal to initiate and coordinate neuronal responses). NGF binding induces TrkA clustering on the membrane and activates the kinase. The kinase initiates a cascade of protein phosphorylation events through multiple pathways including SHC/Ras/MAPK, PI3K and PLCg1. A TrkA kinase inhibitor would not be expected to prevent NGF/TrkA binding, but could prevent down-stream signal transduction.

[0569] Nerve Growth Factor (NGF) is produced by a number of tissues and inflammatory cells during tissue injury and host immune response. It initiates and maintains hypersensitivity to incoming stimulus (hyperalgesia) and the perception of non-noxious stimuli (allodynia). Through its high-affinity receptor TrkA, NGF increases the excitation state of sensory neurons leading to the central nervous system (peripheral sensitization), and increases transmitter release from the dorsal spinal cord (central sensitization). In clinical trials, a single NGF subcutaneous injection generated local hyperalgesia persisting up to 7 weeks. At doses above 0.1 microgram/kg, NGF caused muscle pain that varied from mild to moderate, primarily in the bulbar and truncal musculature. Intravenous NGF produced earlier and more pronounced systemic effects (Petty et al, 1994, Ann Neurol. 36: 244-6). Conversely, TrkA kinase inhibitors could be used to treat diseases of enhanced states of nociception.

[0570] In Complete Freund's Adjuvant (CFA)-induced hind-paw inflammation, spinal nerve ligation and streptozoticin-induced neuropathic pain models, a single intraperitoneal injection of anti-NGF reversed established tactile allodynia from day 3 to day 7 following treatment. In the mouse CCI model, anti-NGF reversed tactile allodynia when administered 2 weeks after surgery. Repeated administration of this antibody to CCI mice for 3 weeks produced a sustained reversal of tactile allodynia (Wild et al, 2007, J. Pharmacol. Exp. Ther. 322:282-287).

[0571] Prostate tumors that have metastasized to bone frequently induce bone pain which can be difficult to fully control as it seems to be driven simultaneously by inflammatory, neuropathic, and tumorigenic mechanisms. Anti-NGF produced a significant reduction in both early and late stage bone cancer pain–related behaviors. This therapy did not influence tumor-induced bone remodeling, osteoblast proliferation, osteoclastogenesis, tumor growth, or markers of sensory or sympathetic innervation in the skin or bone. All nerve fibers that innervate the bone express TrkA and p75, and these are the receptors through which NGF sensitizes and/or activates nociceptors (Halvorson et al, 2005, Cancer Res. 65:9426-35).

[0572] In patients with mild asthma due to exposure to cat allergen, NGF expression was strongly induced in epithelial cells, fibroblasts, blood vessels, and a few infiltrating cells. TrkA mRNA and protein levels in bronchial biopsies were increased significantly after allergen exposure in infiltrating mast cells before the onset of symptoms (Kassel et al, 2001, Clin Exp Allergy 31:1432-40).

[0573] The late phase reaction in asthma following allergen provocation is dominated by an influx of activated eosinophils into the bronchial lumen, which correlates with the release of eosinophilic products into the airways to increase disease severity. The viability and activation of eosinophils from patients with mild asthma were significantly enhanced after NGF stimulation. Addition of neutralizing anti-NGF antibodies *ex vivo* abrogated the effects (Nassentein et al, 2003, J Exp Med 198:455-467). TrkA kinase inhibitors could decrease this paracrine loop between the respiratory tract and infiltrating mast cells as well as endobronchial eosinophils, and thus be useful for the treatment of asthma and other allergic disorders.

[0574] **TrkB:** Target kinase TrkB (i.e., neurotrophic tyrosine kinase, receptor, type 2) is a 145 kDa tyrosine kinase encoded by chromosome 9q22.1 (symbol: NTRK2). TrkB inhibitors may be useful in treating various cancers and their metastases (e.g. prostate cancer, lung cancer, Wilms tumors, neuroblastoma, and pancreatic cancer), and various neuropathies (e.g. stroke, multiple sclerosis, transverse myelitis, and encephalitis).

[0575] In clinical trials with recombinant BDNF, paresthesia was developed at the site of subcutaneous injection (Coulie et al, 2000, Gastroenterology 119:41-50). Intrathecal infusion of BDNF in humans also induced paresthesia and warmth as side effects (Ochs et al, 2000, Amyotroph Lateral Scler Other Motor Neuron Disord. 1:201-6). Chronic paresthesia is often a symptom of an underlying neurological disease or traumatic nerve damage. Paresthesia can be caused by disorders affecting the central nervous system, such as stroke and transient ischemic attacks (mini-strokes), multiple sclerosis, transverse myelitis, and encephalitis. Since BDNF binds to TrkB specifically with high affinity these neuropath effects are mediated through TrkB signaling. Thus Trkb kinase inhibitors could be used to treat certain patients with neuropathy.

[0576] BDNF is known to act at the synapses between primary sensory and spinal dorsal horn neurons to affect pain transmission during inflammation. The primary afferent is the only source of BDNF in the spinal cord, and it is up-regulated in the dorsal root ganglion (DRG) by peripheral NGF a few days after inflammation, and is transported and released into the superficial dorsal horn in an activity-dependent manner. TrkB expression in the dorsal horn also increases for a few days after inflammation. These findings suggest that BDNF may act during the restricted period in the early phase of inflammation. Through TrkB, BDNF activates two distinct channels: (1) transient receptor potential canonicals (TRPC3), which produces a slow response by opening of a non-selective cation channel; and (2) Na+ channel, which mediates a rapid depolarization in the hippocampus. These channels have been strongly associated with inflammatory pain. Anti-BDNF significantly increased the withdrawal threshold in CFA-treated rats, a model of inflammatory pain. Since the swelling at the site of CFA injection was not affected by antiserum, the residual component might be due to peripheral sensitization (Matayoshi et al, 2005, J Physiol. 569:685-95).

[0577] In patients with neuroblastomas, co-expression of TrkB and BDNF, co-expression of TrkB with N-Myc amplification, and expression of truncated TrkB are found to be associated with poorer clinical outcome (Nakagawara et al, 1994, Mol Cell Biol. 14:759-767). Co-expression of TrkB with its ligand BDNF could generate a positive feedback loop through autocrine and paracrine loops. Also TrkB truncations found in these tumors generate activated forms of the intracellular protein tyrosine kinase. The constitutively active TrkB signals through multiple pathways to promote cancer initiation, progression and metastasis. These truncated TrkB kinases were also found in hepatocellular carcinoma (Yang et al, 2005, Cancer. Res 65:219-225). Thus TrkB inhibitors could be used to treat a sub-population of cancer patients with an activated TrkB pathway.

[0578] In patients with pancreatic cancer, TrkB expression is correlated with perineural invasion, positive retroperitoneal margin, and shorter latency to development of liver metastasis (Sclabas et al, 2005, Clin. Cancer. Res V11:440-449). Mechanistically, TrkB activates the PI3K pathway to suppress anoikis (apoptosis resulting from loss of cell-matrix interactions) which is one of the physiological barriers to metastasis. TrkB kinase inhibition could break down resistance to anoikis of metastasizing tumors (Douma et al, 2004, Nature 430:1034-9). Therefore, TrkB inhibitors could have utility in a broad range of tumor types.

[0579] **TrkC:** Target kinase TrkC (i.e., neurotrophic tyrosine kinase, receptor, type 3) is a 145 kDa tyrosine kinase encoded by chromosome 15q25 (symbol: NTRK3). TrkC inhibitors may be useful in treating pain (e.g. chronic pain, neuropathic pain), cancer (e.g. lung cancer, breast cancer, pancreatic cancer, mesoblastic nephroma, infantile fibrosarcoma, neuroblastoma, gastric cancer), and panic disorder.

[0580] Involvement of TrkC in the molecular and cellular changes underlying panic attacks and opiate dependence has been indicated (Gallego et al., Front Behav. Neurosci., 2010, 3:60). TrkC expression in mechanosecnsory neurons suggests a role for TrkC inhibition in treatment of pain (J Comp. Neurol., 2008, 511(4):543-56.

[0581] TrkC is also involved in a variety of cancers, for example neuroblastoma (J. Clin. Invest., 2010, 120(3):850-8), mesoblastic nephroma, infantile fibrosarcoma, and secretory breast cancer, where ETV6-NTRK3 gene fusion is present (Pediatr. Radiol. 2009, 39(10):1066-74; J. Clin. Pathol. 2009, 62(7):604-12) and cancers involving mutations in TrkC, such as lung cancer, gastric cancer, and pancreatic cancer (Marchetti et al., Hum. Mutat. 2008, 29(5):609-16; Kubo et al., Carcinogenesis, 2009, 30(11):1857-64); and Kubo et al., Pancreas, 2009, 38(7):e200-6).

Kinase Activity Assays

[0582] 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.

[0583] 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

[0584] 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

[0585] 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

[0586] 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.

[0587] Prodrugs are compounds or pharmaceutically acceptable salts thereof which, when metabolized under physiological conditions or when converted by solvolysis, yield the desired active compound. Prodrugs include, without limitation, esters, amides, carbamates, carbonates, ureides, solvates, or hydrates of the active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide one or more advantageous handling, administration, and/or metabolic properties. For example, some prodrugs are esters of the active compound; during metabolysis, the ester group is cleaved to yield the active drug. Esters include, for example, esters of a carboxylic acid group, or S-acyl or O-acyl derivatives of thiol, alcohol, or phenol groups. In this context, a common example is an alkyl ester of a carboxylic acid. Prodrugs may also include variants wherein an -NH group of the compound has undergone acylation, such as the 1-position of the 1H-pyrrolo[2,3-b]pyridine ring or the 7-position of the 7H-pyrrolo[2,3-d]pyrimidine of compounds of Formula I, 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.

[0588] 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:

[0589] 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.

[0590] 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.

[0591] 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.

[0592] 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*.

[0593] 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.

[0594] 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

[0595] 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.

[0596] 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, or on carbon atoms of a cycloalkyl. 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.

[0597] 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

[0598] Unless specified to the contrary, specification of a compound herein includes pharmaceutically acceptable salts of such compound. Thus, compounds of Formula I 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.

[0599] 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.

[0600] 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.

[0601] 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

[0602] 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.

[0603] 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.

[0604] 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

[0605] 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 of Formula I or any of the subformulas as described herein, or any of the compounds disclosed in any of the embodiments and examples, and pharmaceutically acceptable salts or solvates thereof 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).

[0606] 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, hypromellose, and the like.

[0607] 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 of Formula I 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.

[0608] Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.5 mg to 1 g, preferably 1 mg to 700 mg, more preferably 5 mg to 100 mg of a compound of the invention (as a free-base, solvate (including hydrate) or salt, in any form), depending on the condition being treated, the route of administration, and the age, weight and condition of the patient. Preferred unit dosage formulations are those containing a daily dose, weekly dose, monthly dose, a sub-dose or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

[0609] 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.

[0610] In some embodiments, injection (parenteral administration) may be used, *e.g.,* intramuscular, intravenous, intraperitoneal, and/or subcutaneous. Compounds of Formula I 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.

[0611] In some embodiments, transmucosal, topical or transdermal administration may be used. In such formulations of compounds of Formula I, 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 of Formula I 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.

[0612] In some embodiments, compounds are administered as inhalants. Compounds of Formula I 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 of Formula I 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.

[0613] 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.

[0614] The compounds of Formula I 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.

[0615] 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 of Formula I, or at the same time as a compound of Formula I. 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 of Formula I 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 of Formula I 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 of Formula I 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 of Formula I. 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 of Formula I 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

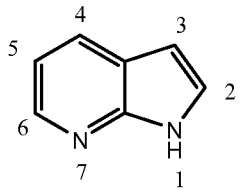
compounds may have a linkage that is substantially maintained *in vivo*, or the linkage may break down *in vivo*, separating the two active components.

EXAMPLES

[0616] 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.

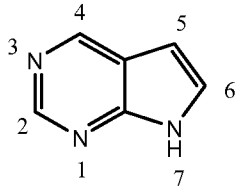
[0617] Unless specifically indicated otherwise, the Formula enumeration and R group enumeration used in the following examples is not related to such enumeration in other sections of this application. The reagents and solvents used in these examples can be readily substituted with appropriate alternatives 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.

[0618] Ring numbering for the 1H-pyrrolo[2,3-b]pyridine in the following Examples is as follows:



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[0619] Ring numbering for the 7H-pyrrolo[2,3-d]pyrimidine in the following Examples is as follows:

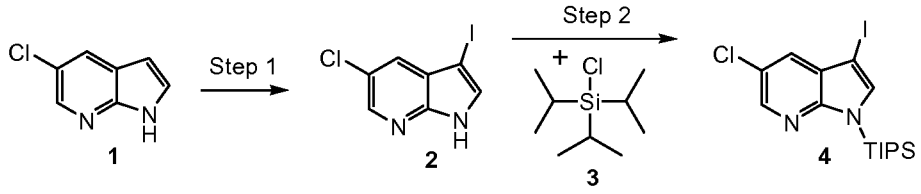


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Example 1: Synthesis of 5-chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine 4.

[0620] 5-Chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **4** is prepared in two steps from 5-chloro-1H-pyrrolo[2,3-b]pyridine **1** as shown in Scheme 1.

Scheme 1



Step 1 – Preparation of 5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (2):

[0621] To a solution of 5-chloro-1H-pyrrolo[2,3-b]pyridine (**1**, 15.00 g, 98.31 mmol) in 300 mL of dichloromethane under an atmosphere or nitrogen, pyridine (7.951 mL, 98.31 mmol) and iodine monochloride (110 mL, 1.0 M in dichloromethane, 110 mmol) are added slowly over 20 minutes. The reaction is stirred at room temperature for 2 hours, then quenched with 100 mL of 1 M aqueous sodium thiosulfate pentahydrate. The layers are separated, solids collected from the aqueous layer by filtration and combined with the organic layer. The aqueous layer is extracted with ethyl acetate, and the organic layers are combined and washed with brine, then concentrated under vacuum. The resulting solid is washed with 20% ethyl acetate in hexane to provide the desired compound.

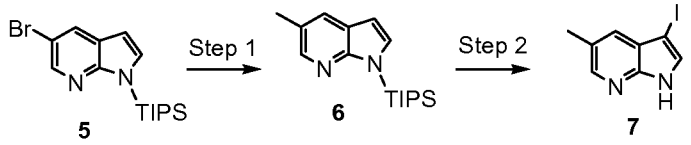
Step 2 – Preparation of 5-chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (4):

[0622] To 5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (**2**, 16.50 g, 59.25 mmol) in 250.0 mL of N,N-dimethylformamide, sodium hydride (3.10 g, 77.5 mmol) is added. The reaction is stirred at room temperature for 90 minutes, then triisopropylsilyl chloride (**3**, 13.00 mL, 61.36 mmol) is added slowly. The reaction is stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**4**, 10.0 g).

Example 2: Synthesis of 3-iodo-5-methyl-1H-pyrrolo[2,3-b]pyridine 7.

[0623] 3-Iodo-5-methyl-1H-pyrrolo[2,3-b]pyridine **7** is prepared in two steps from 5-bromo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **5** as shown in Scheme 2.

Scheme 2



*Step 1 – Preparation of 5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**6**):*

[0624] In a round bottom flask, [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) 1:1 complex with dichloromethane (0.04 g, 0.05 mmol) is combined with 10 mL of toluene under an atmosphere of nitrogen, and 5-bromo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**5**, 0.3 g, 0.8 mmol) in 1 mL of toluene is added dropwise. The reaction is stirred at 60 °C for 1 hour, then at 90 °C for 30 minutes. The reaction is cooled to room temperature, an ice/water solution of 0.1 N citric acid at pH 4 is added, and the mixture extracted with ethyl acetate. The organic layer is washed with brine, de-colored with charcoal, filtered through celite and the filtrate dried over sodium sulfate. The sodium sulfate is removed by filtration and the filtrate concentrated under vacuum to provide the desired compound (**6**, 218 mg).

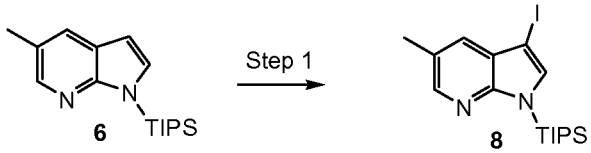
Step 2 – Preparation of 3-iodo-5-methyl-1H-pyrrolo[2,3-b]pyridine (7):

[0625] To a solution of 5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**6**, 1 g, 2.0 mmol) in 10 mL of tetrahydrofuran, iodine (0.43 g, 1.7 mmol) in 5 mL of tetrahydrofuran is added. The reaction is stirred at room temperature overnight, then quenched with 20 mL of 1M aqueous sodium thiosulfate and extracted with ethyl acetate. The organic layers are combined and washed with water and brine, dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with ethyl acetate and hexanes. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound as a white solid (**7**, 20 mg). MS (ESI) $[M+H^+]^+ = 258.70$.

Example 3: Synthesis of 3-iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine 8.

[0626] 3-Iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **8** is prepared in one step from 5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **6** as shown in Scheme 3.

Scheme 3



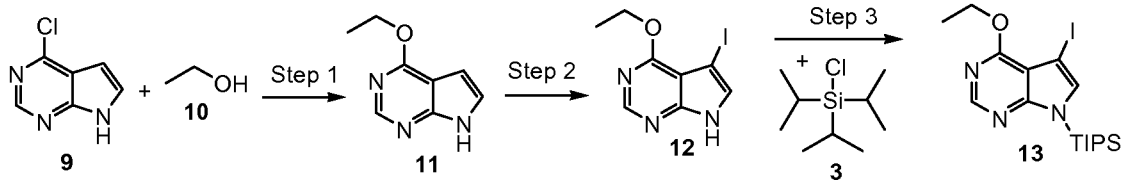
*Step 1 – Preparation of 3-iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**8**):*

[0627] 5-Methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**6**, 1.1 g, 3.8 mmol) and 10 mL of dichloromethane are combined in a round bottom flask and stirred for 10 minutes. A slurry of N-iodosuccinimide (1.0 g, 4.6 mmol) in 5 mL of dichloromethane is added and stirred at room temperature overnight. The reaction is quenched with sodium thiosulfate (20 mL, 1M in water) and the aqueous layer is extracted with ethyl acetate. The combined organic layer is washed with water and 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 hexanes. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound as a light yellow oil (**8**, 1.2 g, 75%). MS (ESI) $[M+H^+]^+ = 415.08$.

Example 4: Synthesis of 4-ethoxy-5-iodo-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidine 13.

[0628] 4-Ethoxy-5-iodo-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidine **13** is prepared in three steps from 4-chloro-7H-pyrrolo[2,3-d]pyrimidine **9** as shown in Scheme 4.

Scheme 4



*Step 1 – Preparation of 4-ethoxy-7H-pyrrolo[2,3-d]pyrimidine (**11**):*

[0629] 4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (**9**, 300 mg, 1.95 mmol) is combined with 3.00 mL of ethanol (**10**, 51.4 mmol), then potassium hydroxide (0.226 g, 4.03 mmol) is added. The reaction is heated at 120 °C for 3 hours in a microwave, then extracted with ethyl acetate and aqueous saturated ammonium chloride. The organic layer is washed with brine, dried with magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is recrystalized from methanol to provide the desired compound (**11**, 213 mg). MS (ESI) $[M+H^+]^+ = 164.9$.

*Step 2 – Preparation of 4-ethoxy-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (**12**):*

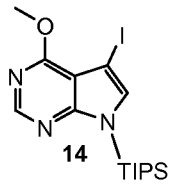
[0630] To 4-ethoxy-7H-pyrrolo[2,3-d]pyrimidine (**11**, 1.60 g, 9.8 mmol) in 50.0 mL of dichloromethane, N,N-dimethylformamide (2.0 mL, 26 mmol) and N-iodosuccinimide (2.40 g, 10.7 mmol) are added and the reaction stirred at room temperature for 2 hours. The reaction is poured into water and extracted with ethyl acetate. The organic layer is dried with sodium sulfate, filtered and the filtrate concentrated under vacuum to provide the desired compound (**12**, 2.70 g).

*Step 3 – Preparation of 4-ethoxy-5-iodo-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidine (**13**):*

[0631] To 4-ethoxy-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (**12**, 2.70 g, 9.34 mmol) in 60.0 mL of tetrahydrofuran under an atmosphere of nitrogen, sodium hydride (411.0 mg, 10.27 mmol) is added.

The reaction is stirred at room temperature for 20 minutes, then triisopropylsilyl chloride (**3**, 2.177 mL, 10.27 mmol) is added. The reaction is stirred at room temperature for 2 hours, then poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 5-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**13**, 3.90 g).

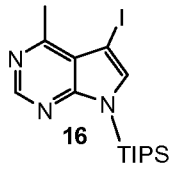
[0632] 5-Iodo-4-methoxy-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidine **14**



14

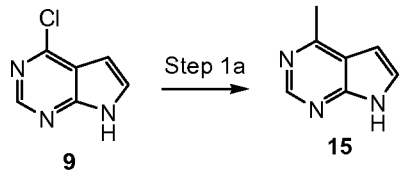
is prepared similarly to the protocol of Scheme 4, replacing ethanol with methanol in step 1.

[0633] 5-Iodo-4-methyl-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidine **16**



16

is prepared similarly to the protocol of Scheme 4, where step 1 is replaced by the following step 1a:

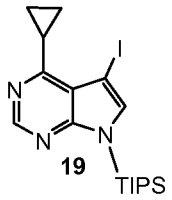


9 **15**

*Step 1a – Preparation of 4-methyl-7H-pyrrolo[2,3-d]pyrimidine (**15**):*

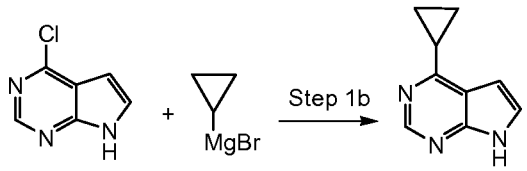
[0634] To 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**9**, 5.03 g, 32.8 mmol) in 100 mL of toluene, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) 1:1 complex with dichloromethane (0.627 g, 0.328 mmol) is added under an atmosphere of nitrogen. After stirring for 10 minutes, methylmagnesium bromide (62.9 mL, 3.00 M in ether, 189 mmol) is added slowly. The reaction is heated at 55 °C overnight, then cooled to -70 to -80 °C and quenched by adding ammonium chloride dropwise. Then 1N hydrochloric acid is added and the pH is adjusted to 7-8 with the addition of saturated sodium bicarbonate. This is extracted 3x with ethyl acetate. The combined organic layer is washed with saturated ammonium chloride and 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 dichloromethane, then methanol and dichloromethane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound as a tan solid (**15**). MS (ESI) $[M+H^+]^+ = 134$. This is reacted similarly to steps 2 and 3 of Scheme 4 to provide the desired compound **16**.

[0635] 4-Cyclopropyl-5-iodo-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidine **19**



19

is prepared similarly to the protocol of Scheme 4, where step 1 is replaced by the following step 1b:

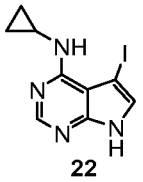


9 **17** **18**

*Step 1b – Preparation of 4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidine (**18**):*

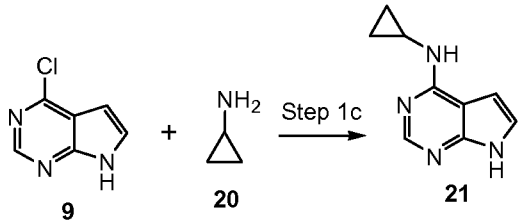
[0636] 4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (**9**, 0.452 g, 2.94 mmol), cyclopropylmagnesium bromide (**17**, 31.4 mL, 0.50 M in tetrahydrofuran, 15.7 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) 1:1 complex with dichloromethane (0.240 g, 0.294 mmol) are combined with 15.4 mL of toluene. The reaction is heated at 60 °C overnight, then quenched with 1 M aqueous hydrochloric acid to pH 4 and filtered through a bed of celite. The layers of the filtrate are separated and the aqueous layer extracted with ethyl acetate. The combined organic layers are washed with brine, dried over sodium 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 (**18**, 0.465 g). MS (ESI) $[M+H^+]^+$ = 160.1. This is reacted similarly to steps 2 and 3 of Scheme 4 to provide the desired compound **19**.

[0637] Cyclopropyl-(5-iodo-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine **22**



22

is prepared similarly to the protocol of scheme 4, steps 1 and 2, where step 1 is replaced by the following step 1c:



9 **20** **21**

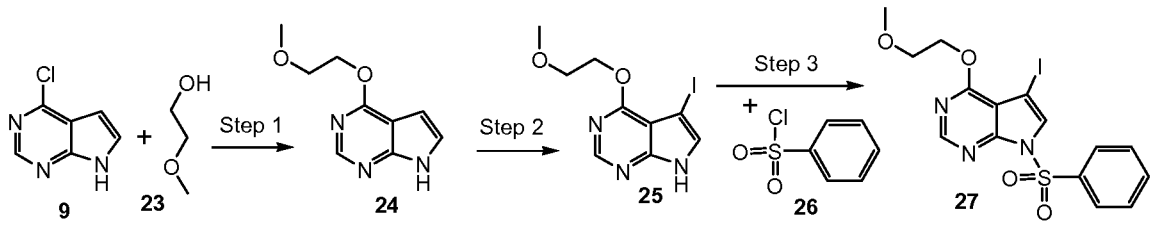
*Step 1c – Preparation of cyclopropyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine (**21**):*

[0638] 4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (**9**, 1.06 g, 6.90 mmol) is dissolved in cyclopropylamine (**20**, 2.42 mL, 34.5 mmol) and heated to reflux overnight. The reaction mixture is cooled and poured into water, then 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 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 (**21**, 337 mg). MS (ESI) $[M+H^+]^+ = 174.9$. This is reacted similarly to step 2 of Scheme 4 to provide the desired compound **22**.

Example 5: Synthesis of 7-benzenesulfonyl-5-iodo-4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidine 27.

[0639] 7-Benzenesulfonyl-5-iodo-4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidine **27** is prepared in three steps from 4-chloro-7H-pyrrolo[2,3-d]pyrimidine **9** as shown in Scheme 5.

Scheme 5



*Step 1 – Preparation of 4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidine (**24**):*

[0640] To 4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (**9**, 5.00 g, 32.6 mmol) in 12.5 mL of 2-methoxy-ethanol (**23**, 158 mmol), potassium hydroxide (3.3 g, 59 mmol) is added. The reaction is heated at 100 °C overnight, then poured into water and extracted with ethyl acetate. The organic layer is dried with sodium sulfate, filtered and the filtrate concentrated under vacuum to provide the desired compound (**24**, 5.70 g).

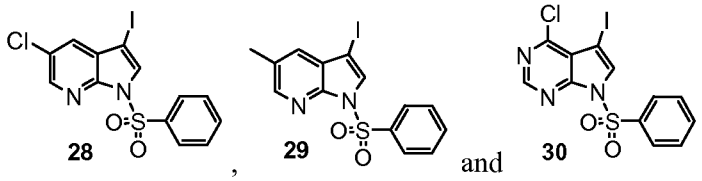
*Step 2 – Preparation of 5-iodo-4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidine (**25**):*

[0641] To 4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidine (**24**, 5.70 g, 29.5 mmol) in 150.0 mL of dichloromethane, N,N-dimethylformamide (6.0 mL, 78 mmol) and N-iodosuccinimide (7.22 g, 32.1 mmol) are added and the reaction stirred at room temperature for 2 hours. The reaction is poured into water and extracted with ethyl acetate. The organic layer is dried with sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is washed with ethyl acetate and hexane to provide the desired compound (**25**, 6.75 g).

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

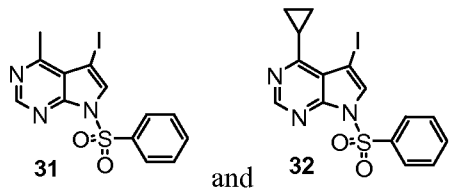
[0642] To 5-iodo-4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidine (**25**, 3.67 g, 11.5 mmol) in 60.0 mL of tetrahydrofuran under an atmosphere of nitrogen, sodium hydride (506.0 mg, 12.65 mmol) is added. The reaction is stirred at room temperature for 20 minutes, then benzenesulfonyl chloride (**26**, 1.614 mL, 12.65 mmol) is added. The reaction is stirred at room temperature for 30 minutes, then poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 15-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**27**, 4.50 g). MS (ESI) $[M+H^+]^+ = 460.0$.

[0643] 1-Benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **28**, 1-benzenesulfonyl-3-iodo-5-methyl-1H-pyrrolo[2,3-b]pyridine **29**, and 7-benzenesulfonyl-4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine **30**,



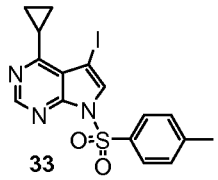
are prepared following the protocol of scheme 5 step 3 or steps 2 and 3, replacing 5-iodo-4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidine **25** with 5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **2** and 3-iodo-5-methyl-1H-pyrrolo[2,3-b]pyridine **7**, respectively in step 3, or by reacting 4-chloro-7H-pyrrolo[2,3-d]pyrimidine **9** directly in step 2.

[0644] 7-Benzenesulfonyl-5-iodo-4-methyl-7H-pyrrolo[2,3-d]pyrimidine **31** and 7-benzenesulfonyl-4-cyclopropyl-5-iodo-7H-pyrrolo[2,3-d]pyrimidine **32**,



are prepared following the protocol of scheme 5 steps 2 and 3, replacing 4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidine **24** with 4-methyl-7H-pyrrolo[2,3-d]pyrimidine **15** and 4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidine **18**, respectively, in step 2.

[0645] 4-Cyclopropyl-5-iodo-7-(toluene-4-sulfonyl)-7H-pyrrolo[2,3-d]pyrimidine **33,**



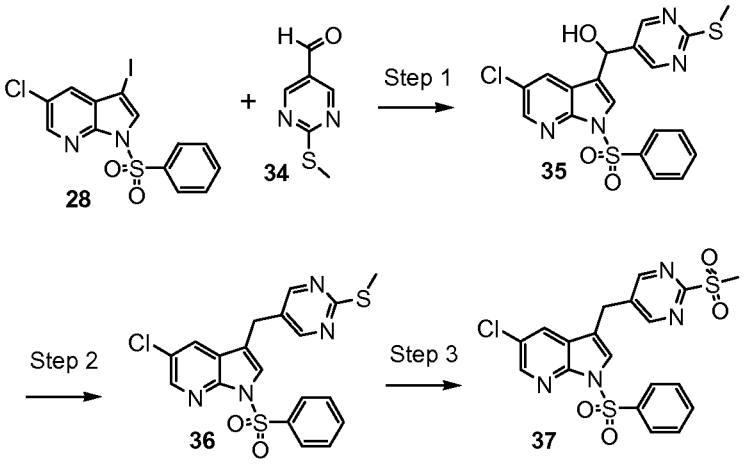
33

is synthesized similarly to compound **32**, where 4-methylbenzenesulfonyl chloride is used in place of benzenesulfonyl chloride **26** in step 3 of Scheme 5.

Example 6: Synthesis of 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine 37.

[0646] 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **37** is prepared in three steps from 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **28** and 2-methylsulfanyl-pyrimidine-5-carbaldehyde **34** as shown in Scheme 6.

Scheme 6



*Step 1 – Preparation of (1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-(2-methylsulfanyl-pyrimidin-5-yl)-methanol (**35**):*

[0647] To a solution of 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (**28**, 8.40 g, 20.1 mmol) in 96.3 mL of tetrahydrofuran at -40 °C under nitrogen, isopropylmagnesium chloride (10.1 mL, 2.0 M in tetrahydrofuran, 20.3 mmol) is added slowly. The reaction is allowed to warm to 5 °C over 60 minutes, then cooled to -40 °C, followed by addition of 2-methylsulfanyl-pyrimidine-5-carbaldehyde (**34**, 2.50 g, 16.2 mmol) in 15.0 mL of tetrahydrofuran. The reaction is allowed to warm to 10 °C over 2 hours, then poured into aqueous ammonium chloride and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate is concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with 40-100% ethyl acetate in hexane. Appropriate fractions are combined and the solvents removed under vacuum to provide the desired compound as an off-white solid (**35**, 4.0 g). MS (ESI) $[M+H^+]^+ = 447.2$.

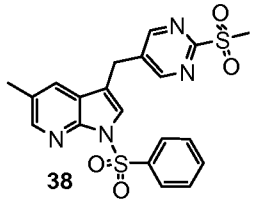
*Step 2 – Preparation of 1-benzenesulfonyl-5-chloro-3-(2-methylsulfanyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**36**):*

[0648] To (1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-(2-methylsulfanyl-pyrimidin-5-yl)-methanol (**35**, 4.70 g, 10.5 mmol) in 120.0 mL of acetonitrile, triethylsilane (22.0 mL, 138 mmol) and trifluoroacetic acid (11.0 mL, 143 mmol) are added. The reaction is stirred at 80 °C for 3 hours, then concentrated under vacuum, mixed with aqueous potassium carbonate and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and solvents removed under vacuum to provide the desired compound (**36**, 2.90 g).

*Step 3 – Preparation of 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**37**):*

[0649] To 1-benzenesulfonyl-5-chloro-3-(2-methylsulfanyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**36**, 4.40 g, 10.2 mmol) in 100.0 mL of dichloromethane, meta-chloroperoxybenzoic acid (max. 77%, 4.90 g, 21.9 mmol) is added at 0 °C. The reaction is stirred at 0 °C for 40 minutes, then poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered, and the filtrate is concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane. Appropriate fractions are combined and solvents removed under vacuum to provide the desired compound (**37**, 3.76 g). MS (ESI) $[M+H^+]^+ = 463.0$.

[0650] 1-Benzenesulfonyl-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-5-methyl-1H-pyrrolo[2,3-b]pyridine **38**



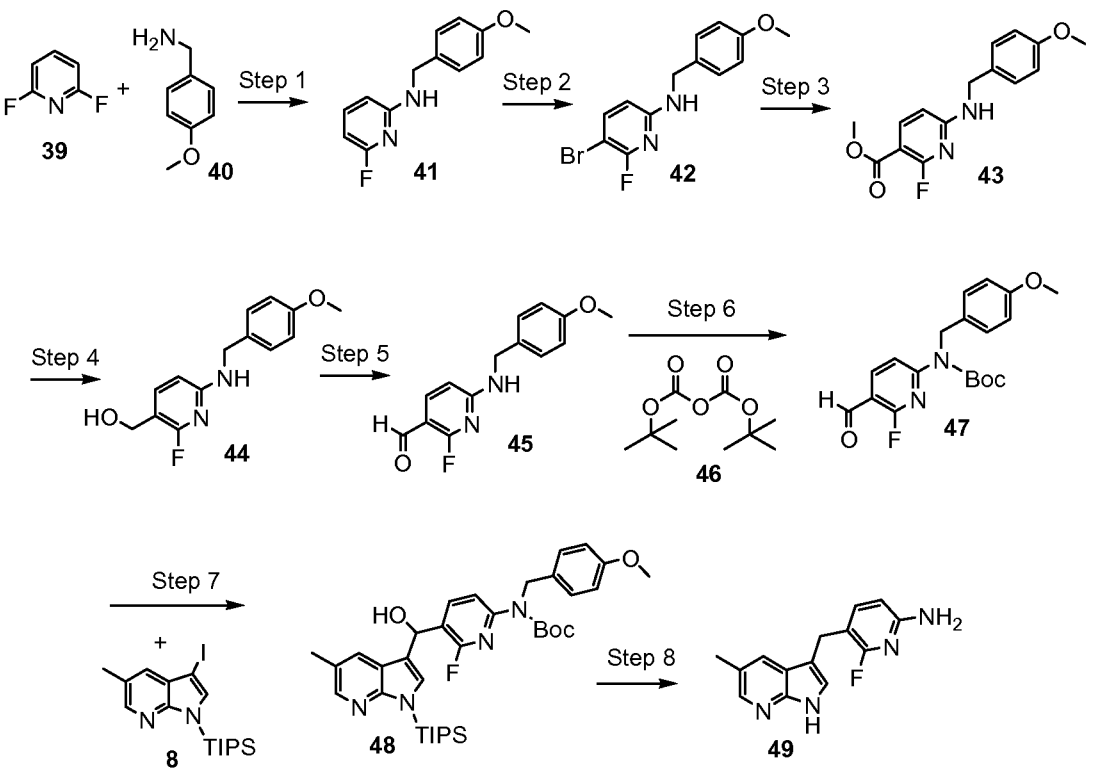
38

is prepared following the protocol of Scheme 6, replacing 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **28** with 1-benzenesulfonyl-3-iodo-5-methyl-1H-pyrrolo[2,3-b]pyridine **29** in step 1.

Example 7: Synthesis of 6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine 49.

[0651] 6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **49** is prepared in seven steps from 2,6-difluoro-pyridine **39** and 4-methoxy-benzylamine **40** as shown in Scheme 7.

Scheme 7



*Step 1 – Preparation of (6-fluoro-pyridin-2-yl)-(4-methoxy-benzyl)-amine (**41**):*

[0652] To 2,6-difluoro-pyridine (**39**, 100 g, 869 mmol) in 500 mL of N-methylpyrrolidinone, 4-methoxy-benzylamine (**40**, 136 mL, 1.043 mol) and N,N-diisopropylethylamine (304 mL, 1.738 mol) are added. The reaction is stirred at 90 °C overnight, then poured into 8 L of water. The resulting precipitate is collected by filtration and washed with water, then taken up in ethyl acetate and washed with water. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is triturated with heptane and collected by filtration to provide the desired compound (**41**, 151 g, 650 mmol, 74.8 % yield).

*Step 2 – Preparation of (5-bromo-6-fluoro-pyridin-2-yl)-(4-methoxy-benzyl)-amine (**42**):*

[0653] To (6-fluoro-pyridin-2-yl)-(4-methoxy-benzyl)-amine (**41**, 151 g, 650 mmol) in 4 L of acetonitrile under an atmosphere of nitrogen, N-bromosuccinimide (116 g, 650 mmol) is added in portions. After reacting for 2 hours, the solvent is removed under vacuum and the residue is taken up in ethyl acetate, then poured into aqueous sodium thiosulfate. The organic layer is washed with warm water, dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is crystallized from heptane to provide the desired compound (**42**, 172 g, 553 mmol, 85 % yield).

*Step 3 – Preparation of 2-fluoro-6-(4-methoxy-benzylamino)-nicotinic acid methyl ester (**43**):*

[0654] To (5-bromo-6-fluoro-pyridin-2-yl)-(4-methoxy-benzyl)-amine (**42**, 85 g, 273 mmol) in 1.5 L of methanol in a 2 L Parr flask, triethylamine (77 mL, 546 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (5.80 g, 7.10 mmol) are added. The reaction is heated at 100 °C under 100 psi of carbon monoxide overnight. The reaction is cooled and filtered through celite and the filtrate is concentrated under vacuum. The resulting material is dissolved in dichloromethane and passed through a plug of silica gel, eluting with ethyl acetate. The solvent is removed under vacuum to provide the desired compound as a peach colored solid (**43**, 70 g, 241 mmol, 88 % yield).

*Step 4 – Preparation of [2-fluoro-6-(4-methoxy-benzylamino)-pyridin-3-yl]-methanol (**44**):*

[0655] To 2-fluoro-6-(4-methoxy-benzylamino)-nicotinic acid methyl ester (**43**, 70 g, 241 mmol) in 350 mL of tetrahydrofuran, lithium aluminum hydride (362 mL, 1 M in tetrahydrofuran, 362 mmol) is added dropwise while cooling. The reaction is stirred at room temperature for 2 hours, then quenched with dropwise addition of 14 mL of water, 14 mL of 15% aqueous sodium hydroxide, and 42 mL of water, sequentially. Then 500 mL of methyl tert-butyl ether is added and solids are removed by filtration. The filtrate is concentrated under vacuum and the resulting solid is dissolved in dichloromethane, passed through a plug of silica gel and eluted with 50-100% ethyl acetate in heptane. The solvent is removed under vacuum to provide the desired compound as an off-white solid (**44**, 63 g, 240 mmol, 100 % yield).

*Step 5 – Preparation of 2-fluoro-6-(4-methoxy-benzylamino)-pyridine-3-carbaldehyde (**45**):*

[0656] To [2-fluoro-6-(4-methoxy-benzylamino)-pyridin-3-yl]-methanol (**44**, 63 g, 240 mmol) in 1.25 L of ethyl acetate, manganese(IV) oxide (210 g, 2.416 mol) is added. The reaction is stirred overnight at room temperature, then filtered through celite and the celite rinsed with ethyl acetate. The combined filtrates are concentrated under vacuum and the resulting solid is triturated with heptane and collected by filtration to provide the desired compound as a white solid (**45**, 62 g, 238 mmol, 99% yield).

*Step 6 – Preparation of (6-fluoro-5-formyl-pyridin-2-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester (**47**):*

[0657] 2-Fluoro-6-(4-methoxy-benzylamino)-pyridine-3-carbaldehyde (**45**, 62 g, 238 mmol), 600 mL of tert-butyl alcohol, di-tert-butyldicarbonate (**46**, 83 mL, 357 mmol) and dimethylaminopyridine (2.91 g, 23.82 mmol) are combined in a round bottom flask. The reaction is stirred at 30 °C overnight and then concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 0-20% ethyl acetate in hexane. Appropriate fractions are combined and the solvents removed under vacuum to provide the desired compound (**47**, 54 g, 150 mmol, 62.9 % yield).

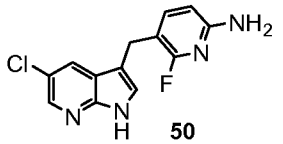
*Step 7 – Preparation of {6-fluoro-5-[hydroxy-(5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl}-(4-methoxy-benzyl)-carbamic acid tert-butyl ester (**48**):*

[0658] To 3-iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**8**, 40 g, 97.0 mmol) in 400 mL of tetrahydrofuran under an atmosphere of nitrogen at -20 °C, isopropylmagnesium chloride (54.8 mL, 2 M in tetrahydrofuran, 110 mmol) is added and the reaction allowed to warm to 0 °C over 30 minutes. The reaction is cooled to -40 °C and (6-fluoro-5-formyl-pyridin-2-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester (**47**, 15.81 g, 43.9 mmol) in tetrahydrofuran is added. The reaction is allowed to warm to 0 °C over an hour, then quenched with brine and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 0-40% ethyl acetate in hexane. Appropriate fractions are combined and the solvents removed under vacuum to provide the desired compound (**48**, 21 g, 32.4 mmol, 73.8 % yield).

*Step 8 – Preparation of 6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**49**):*

[0659] To {6-fluoro-5-[hydroxy-(5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl}-(4-methoxy-benzyl)-carbamic acid tert-butyl ester (**48**, 21 g, 32.4 mmol) in 500 mL of acetonitrile, triethylsilane (51.7 mL, 324 mmol) and trifluoroacetic acid (24.93 mL, 324 mmol) are added. The reaction is stirred at 50 °C for several hours, then concentrated under vacuum, and the residue is taken up in 250 mL of dichloromethane and 250 mL of trifluoroacetic acid is added. The mixture is stirred at reflux for several hours, then concentrated under vacuum. The residue is taken up in ethyl acetate and poured into aqueous potassium carbonate. The organic layer is separated, concentrated under vacuum and purified by silica gel column chromatography, eluting with 0-5% methanol in dichloromethane. Appropriate fractions are combined and the solvents removed under vacuum to provide the desired compound (**49**, 5.2 g, 20.29 mmol, 62.7 % yield).

[0660] 5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-ylamine **50**



50

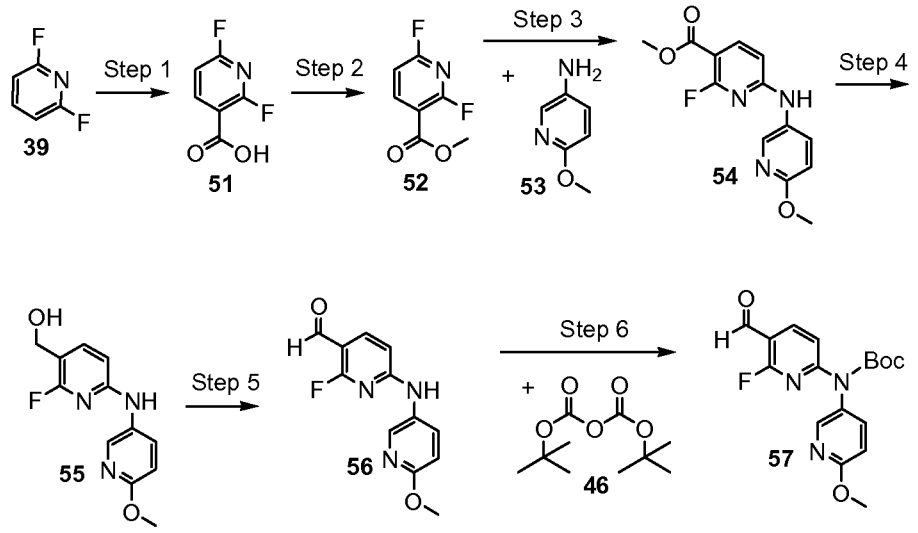
is prepared following the protocol of Scheme 7, replacing 3-iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **8** with 5-chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **4** in step 7.

Example 8: Synthesis of aldehyde reagents.

[0661] Aldehyde reagents that are used in making compounds are prepared according to the following protocols. In these reactions, the unprotected aldehyde isolated after step 5, or the subsequently Boc-protected aldehyde may be used in preparation of compounds.

[0662] (6-ethoxy-pyridin-3-yl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **57** is prepared in six steps from 2,6-difluoro-pyridine **39** as shown in Scheme 8.

Scheme 8



*Step 1 – Preparation of 2,6-difluoro-nicotinic acid (**51**):*

[0663] In a round bottom flask, to 2,6-difluoro-pyridine (**39**, 7.10 g, 61.7 mmol) in 150.0 mL of tetrahydrofuran under an atmosphere of nitrogen at -78 °C, n-butyllithium (26.0 mL, 2.50 M in hexane, 65.0 mmol) is slowly added. After 30 minutes, 3.0 g of dry ice is added and an hour later the reaction is allowed to warm to room temperature. The reaction is poured into water, extracted with ethyl acetate and the aqueous layer is adjusted to pH 4-5 with 1 N hydrochloric acid. This is extracted with ethyl acetate and the organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum to provide the desired compound (**51**, 5.6 g).

*Step 2 – Preparation of 2,6-difluoro-nicotinic acid methyl ester (**52**):*

[0664] In a round bottom flask, 2,6-difluoro-nicotinic acid (**51**, 5.60 g, 35.2 mmol), 60.0 mL of methanol and sulfuric acid (1.0 mL, 19.0 mmol) are combined and heated to reflux overnight. The reaction is poured into water, adjusted to pH around 9 with 1M aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum to provide the desired compound as a yellow oil (**52**, 3.5 g).

*Step 3 – Preparation of 2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-nicotinic acid methyl ester (**54**):*

[0665] To a round bottom flask, 2,6-difluoro-nicotinic acid methyl ester (**52**, 2.00 g, 11.6 mmol) is combined with 20.0 mL of N,N-dimethylformamide under an atmosphere of nitrogen at -40 °C. To this, 5-amino-2-methoxypyridine (**53**, 1.55 g, 12.5 mmol) and triethylamine (5.0 mL, 36.0 mmol) are added and the reaction stirred at -40 °C, then warmed to room temperature and reacted overnight. The reaction is then heated to 50 °C over the weekend, then at 70 °C for 3 hours. The reaction is poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**54**, 1.20 g).

*Step 4 – Preparation of [2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-methanol (**55**):*

[0666] To 2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-nicotinic acid methyl ester (**54**, 1.20 g, 4.33 mmol) in 50.0 mL of tetrahydrofuran, lithium tetrahydroaluminate (8.66 mL, 1.00 M in tetrahydrofuran, 8.66 mmol) is added and the reaction is stirred at room temperature for 3 hours. Sodium sulfate decahydrate (5g) is added and after 1 hour, the reaction is filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**55**, 700 mg). MS (ESI) $[M+H^+]^+ = 250.1$.

*Step 5 – Preparation of 2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridine-3-carbaldehyde (**56**):*

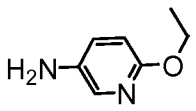
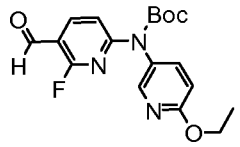
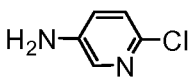
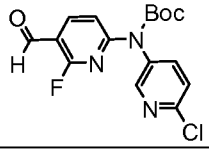
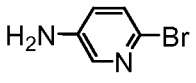
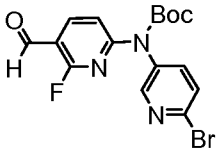
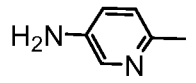
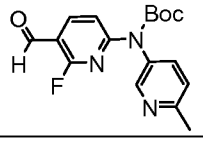
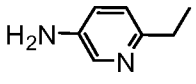
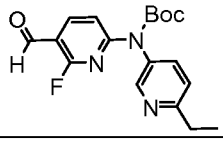
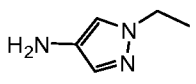
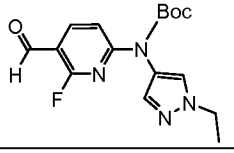
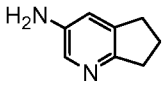
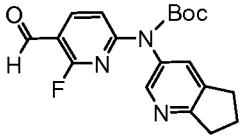
[0667] To [2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-methanol (**55**, 0.700 g, 2.81 mmol) in 20.0 mL of tetrahydrofuran, Dess-Martin periodinane (1.44 g, 3.40 mmol) is added and the reaction stirred at room temperature for 30 minutes. The reaction is poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**56**, 450 mg). MS (ESI) $[M+H^+]^+ = 248.0$.

*Step 6 – Preparation of (6-fluoro-5-formyl-pyridin-2-yl)-(6-methoxy-pyridin-3-yl)-carbamic acid tert-butyl ester (**57**):*

[0668] To 2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridine-3-carbaldehyde (**56**, 2.21 g, 8.94 mmol) in 50 mL of tetrahydrofuran, di-tert-butyldicarbonate (**46**, 2.82 g, 12.9 mmol) and 4-dimethylaminopyridine (0.30 g, 2.4 mmol) are added and the reaction stirred at room temperature overnight. The reaction is concentrated under vacuum and the resulting material is purified by silica gel column chromatography eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**57**, 1.39 g).

[0669] Additional aldehydes are prepared similarly to the protocol of scheme 8, as shown in the following table, replacing 5-amino-2-methoxypyridine **53** with a suitable amine compound in step 3. While the table indicates the Boc-protected aldehyde, the non-Boc protected aldehyde may be isolated after step 5.

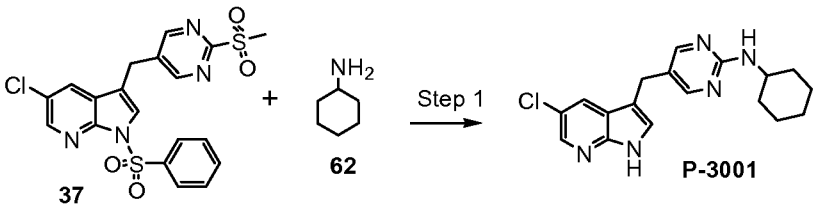
Table 3

Step 3 amine compound	Final aldehyde
	
	
	
	
	
	
	

Example 9: Synthesis of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclohexyl-amine P-3001.

[0670] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclohexyl-amine **P-3001** is prepared in one step from 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **37** and cyclohexanamine **62** as shown in Scheme 9.

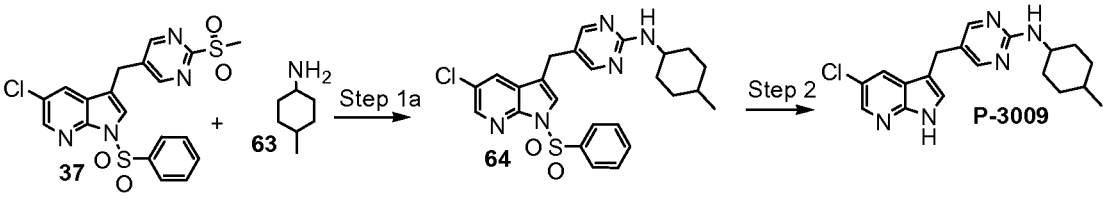
Scheme 9



*Step 1 – Preparation of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclohexyl-amine (**P-3001**):*

[0671] In a microwave vial, to 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**37**, 60 mg, 0.13 mmol) in 1.0 mL of N-methylpyrrolidinone, cyclohexanamine (**62**, 0.20 g, 2.0 mmol) is added. The reaction is heated at 155 °C for 25 minutes in a microwave, then potassium hydroxide (1.0 mL, 1.00 M in water, 1.0 mmol) is added and the reaction heated at 95 °C for 15 minutes in a microwave. The reaction is poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are collected and concentrated under vacuum to provide the desired compound (**P-3001**, 11.4 mg). MS (ESI) $[M+H^+]^+$ = 341.9.

[0672] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methyl-cyclohexyl)-amine **P-3009** was prepared similarly to Scheme 9, replacing step 1 with the following steps 1a and 2:



*Step 1a – Preparation of [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methyl-cyclohexyl)-amine (**64**):*

[0673] In a microwave vial, to 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**37**, 0.140 g, 0.302 mmol) in 2.0 mL of N-methylpyrrolidinone, 4-methylcyclohexylamine (**63**, 0.30 g, 2.6 mmol) is added. The reaction is heated at 160 °C for 20 minutes in a microwave, then poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**64**, 0.120 g). MS (ESI) $[M+H^+]^+$ = 496.4.

*Step 2 – Preparation of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methyl-cyclohexyl)-amine (**P-3009**):*

[0674] To [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methyl-cyclohexyl)-amine (**64**, 0.120 g, 0.242 mmol) in 5.0 mL of tetrahydrofuran, tetrabutylammonium fluoride trihydrate (0.20 g, 0.63 mmol) is added. The reaction is stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are collected and concentrated under vacuum to provide the desired compound (**P-3009**, 1.4 mg). MS (ESI) $[M+H^+]^+ = 355.95$.

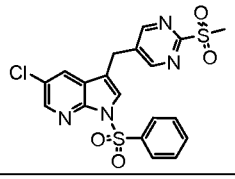
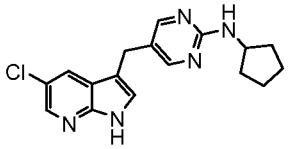
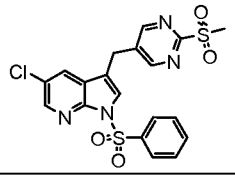
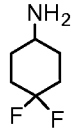
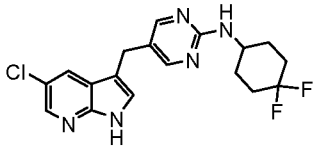
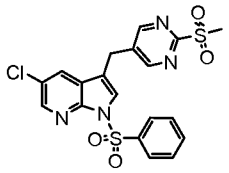
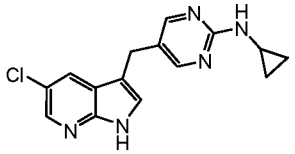
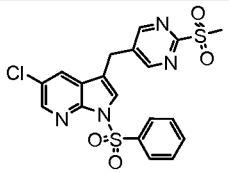
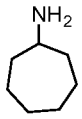
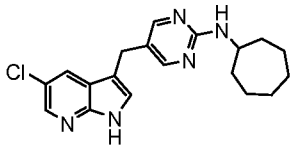
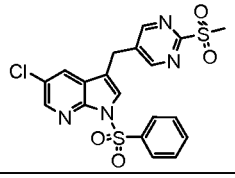
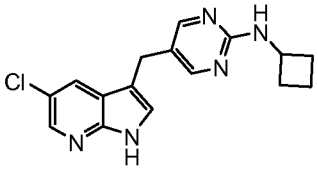
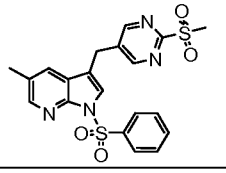
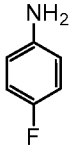
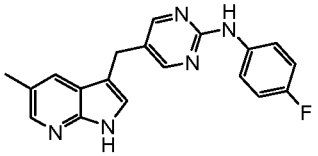
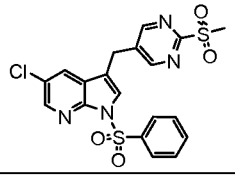
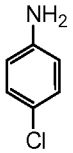
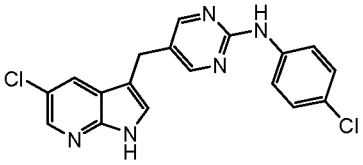
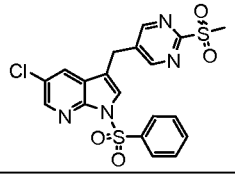
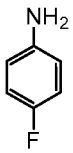
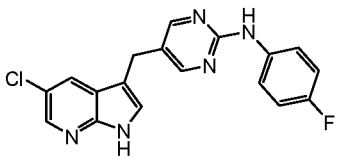
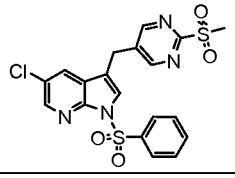
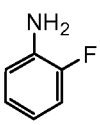
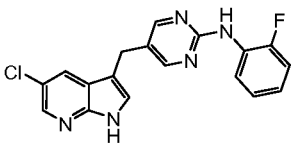
[0675] Additional compounds are prepared following the protocol of Scheme 9. Compounds are made substituting cyclohexanamine **62** with a suitable amine and optionally substituting 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **37** with 1-benzenesulfonyl-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-5-methyl-1H-pyrrolo[2,3-b]pyridine **38**. The following compounds are made using this procedure:
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclopentyl-amine (**P-3003**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4,4-difluoro-cyclohexyl)-amine (**P-3004**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclopropyl-amine (**P-3005**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cycloheptyl-amine (**P-3006**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclobutyl-amine (**P-3007**),
(4-Fluoro-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3010**),
(4-Chloro-phenyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3011**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine (**P-3012**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-phenyl)-amine (**P-3014**),
(2-Chloro-phenyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3015**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-phenyl)-amine (**P-3016**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-phenyl)-amine (**P-3017**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-yl)-amine (**P-3018**),
(6-Methoxy-pyridin-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine

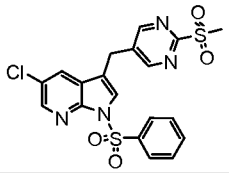
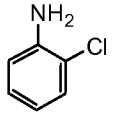
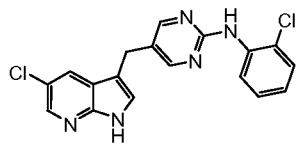
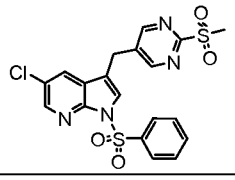
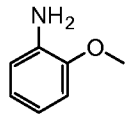
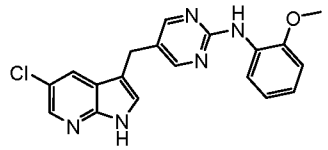
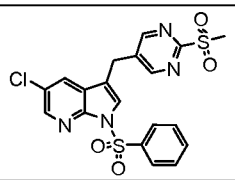
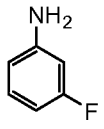
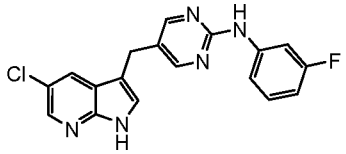
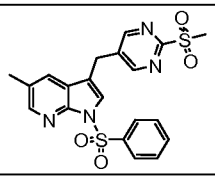
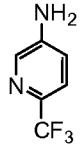
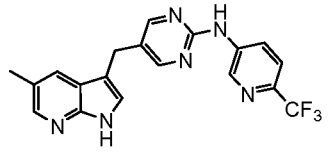
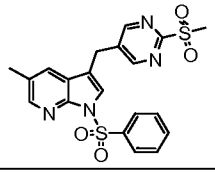
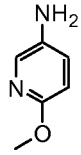
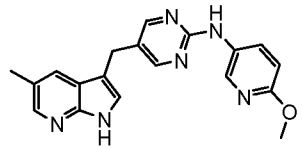
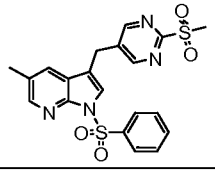
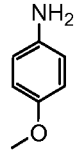
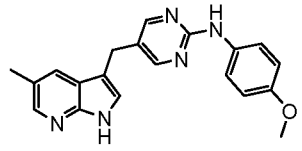
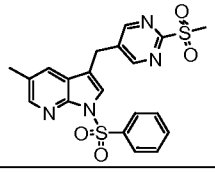
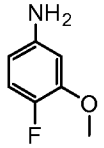
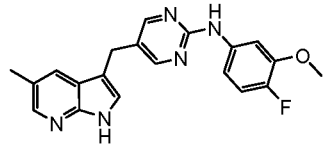
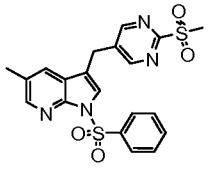
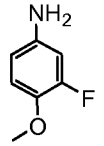
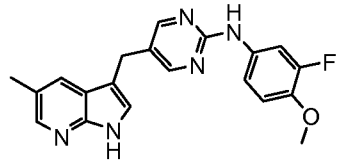
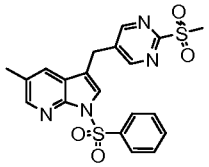
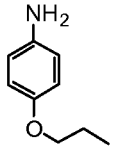
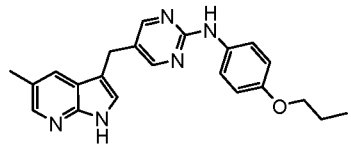
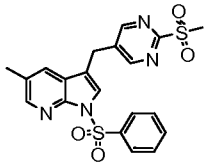
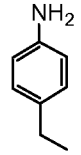
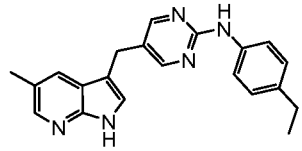
(**P-3020**),
(4-Methoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3021**),
(4-Fluoro-3-methoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3022**),
(3-Fluoro-4-methoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3023**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-propoxy-phenyl)-amine (**P-3024**),
(4-Ethyl-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3025**),
(4-Ethoxy-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3026**),
(6-Ethoxy-pyridin-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3027**),
[5-(4-Fluoro-phenyl)-2H-pyrazol-3-yl]-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3028**),
(5-tert-Butyl-2H-pyrazol-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3029**),
(4-tert-Butyl-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine amine (**P-3030**),
1,1,1,3,3,3-Hexafluoro-2-{4-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-ylamino]-phenyl}-propan-2-ol (**P-3031**),
(5-Cyclopropyl-2H-pyrazol-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3032**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methylsulfanyl-phenyl)-amine (**P-3033**),
(1-Ethyl-1H-pyrazol-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3035**),
(1-Ethyl-1H-pyrazol-4-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3036**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-trifluoromethyl-2H-pyrazol-3-yl)-amine (**P-3037**), and
(5-Isopropoxy-2H-pyrazol-3-yl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-3038**).

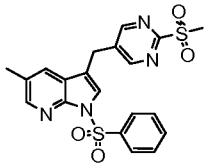
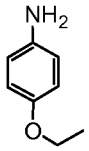
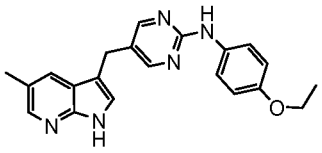
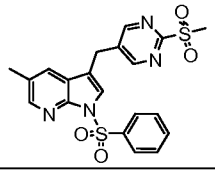
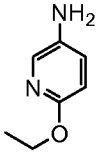
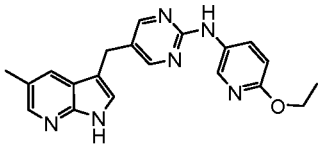
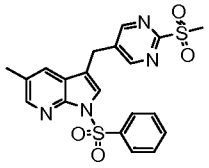
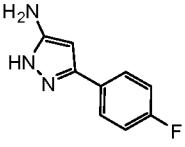
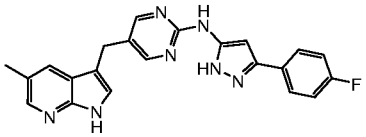
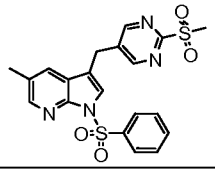
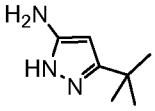
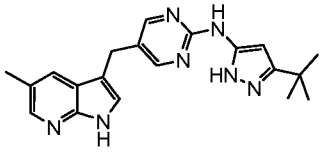
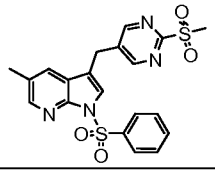
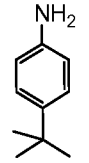
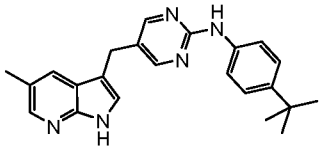
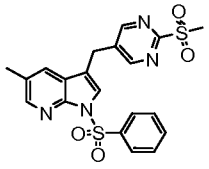
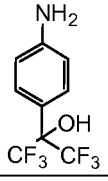
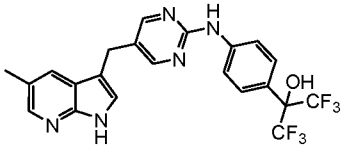
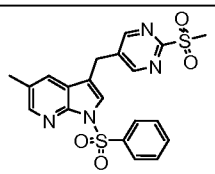
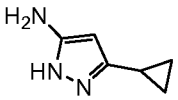
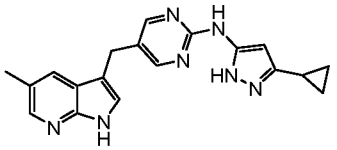
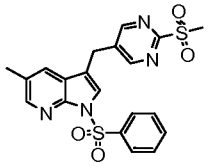
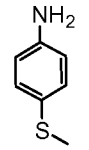
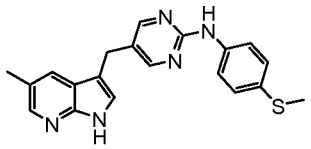
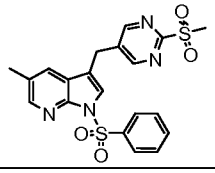
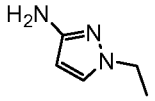
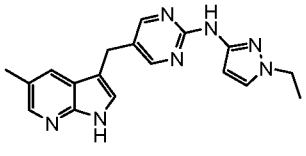
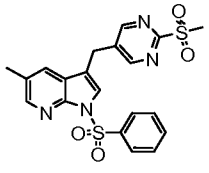
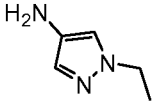
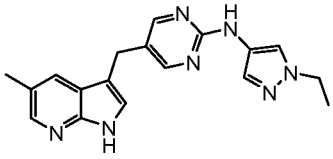
The following table indicates the 2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (column 2) and amine compound (column 3) used in step 1 to afford the desired compound

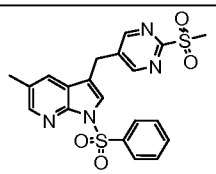
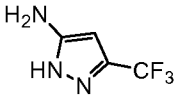
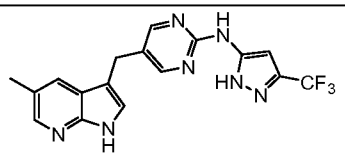
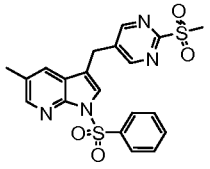
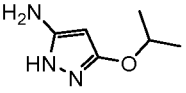
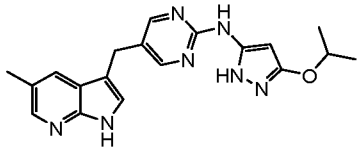
(column 4). The compound number is provided in column 1, and the observed mass is in column 5.

Table 4

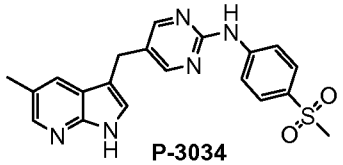
Comp. number	pyrrolo[2,3-b]pyridine	Amine structure	Compound structure	MS (ESI) $[M+H^+]^+$
P-3003				328.0
P-3004				377.9
P-3005				300.0
P-3006				356.3
P-3007				314.2
P-3010				334.1
P-3011				370.8
P-3012				354.0
P-3014				353.9

P-3015				369.9
P-3016				365.9
P-3017				353.9
P-3018				384.9
P-3020				347.1
P-3021				346.2
P-3022				363.9
P-3023				363.9
P-3024				374.0
P-3025				344.0

P-3026				360.0
P-3027				501.3
P-3028				399.9
P-3029				362.0
P-3030				372.0
P-3031				482.3
P-3032				346.0
P-3033				362.1
P-3035				334.2
P-3036				333.9

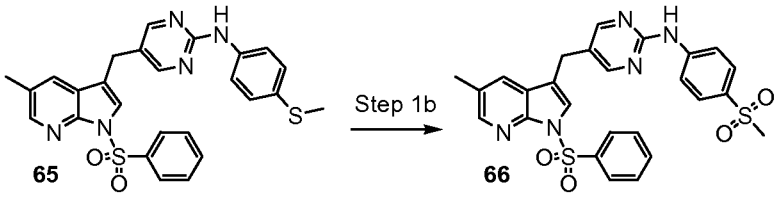
P-3037				374.0
P-3038				363.9

[0676] (4-Methanesulfonyl-phenyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **P-3034**



P-3034

is prepared by oxidizing the product of Scheme 9 step 1a in the preparation of [5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methylsulfanyl-phenyl)-amine (**P-3033**), prior to reaction of step 2, according to the following step 1b:



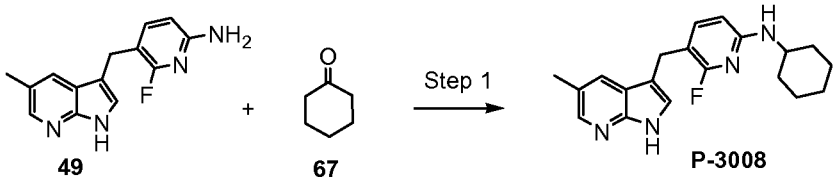
*Step 1b – Preparation of [5-(1-benzenesulfonyl-5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methanesulfonyl-phenyl)-amine (**66**):*

[0677] To [5-(1-benzenesulfonyl-5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methylsulfanyl-phenyl)-amine (**65**, 80 mg, 0.16 mmol) in 10.0 mL of dichloromethane, meta-chlorperoxybenzoic acid (78.6 mg, 0.351 mmol) is added at 0 °C. The reaction is stirred at room temperature for 30 minutes, then concentrated under vacuum to provide [5-(1-benzenesulfonyl-5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methanesulfonyl-phenyl)-amine **66**, which is reacted according to Scheme 9 step 2 to provide the desired compound (**P-3034**, 30.7 mg). MS (ESI) $[M+H^+]^+ = 393.9$.

Example 10: Synthesis of cyclohexyl-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-3008.

[0678] Cyclohexyl-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-3008** is prepared in one step from 6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **49** and cyclohexanone **67** as shown in Scheme 10.

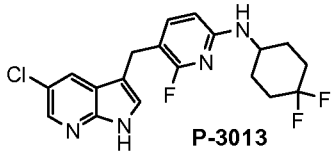
Scheme 10



*Step 1 – Preparation of cyclohexyl-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3008**):*

[0679] To 6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**49**, 100 mg, 0.39 mmol) and cyclohexanone (**67**, 0.0465 mL, 0.449 mmol) in 3.00 mL of acetonitrile, triethylsilane (0.400 mL, 2.50 mmol) and trifluoroacetic acid (0.300 mL, 3.89 mmol) were added. The reaction was stirred at 80 °C overnight, then extracting with ethyl acetate and 1N aqueous sodium bicarbonate. The organic layer was washed with brine, dried with magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 0-60% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**P-3008**, 115 mg). MS (ESI) $[M+H^+]^+ = 339.0$.

[0680] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(4,4-difluoro-cyclohexyl)-amine **P-3013**

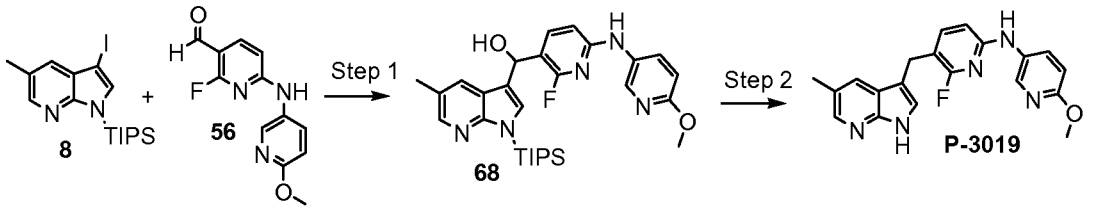


is prepared following the protocol of Scheme 10, replacing 6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **49** with 5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-ylamine **50** and replacing cyclohexanone **67** with 4,4-difluoro-cyclohexanone. MS (ESI) $[M+H^+]^+ = 394.9$ and 396.9.

Example 11: Synthesis of [6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine P-3019.

[0681] [6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine **P-3019** is prepared in two steps from 3-iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **8** and 2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridine-3-carbaldehyde **56** as shown in Scheme 11.

Scheme 11



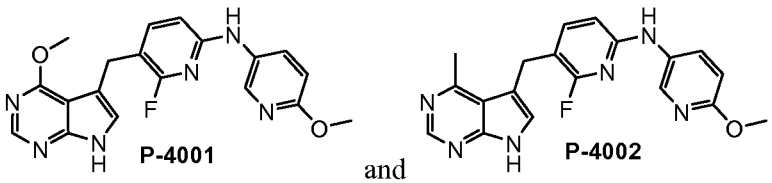
*Step 6 – Preparation of [2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-(5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**68**):*

[0682] To a solution of 3-iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**8**, 1.02 g, 2.461 mmol) in 6.0 mL of tetrahydrofuran at -50 °C under nitrogen, isopropylmagnesium chloride (1.23 mL, 2.00 M in tetrahydrofuran, 2.46 mmol) is added slowly. The reaction is allowed to warm to 5 °C over 70 minutes, then cooled to -45 °C, followed by addition of 2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridine-3-carbaldehyde (**56**, 0.165 g, 0.667 mmol) in 2.0 mL of tetrahydrofuran. The reaction is allowed to warm to room temperature over an hour, then poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**68**, 330 mg). MS (ESI) $[M+H^+]^+ = 536.2$.

*Step 7 – Preparation of [6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-3019**):*

[0683] To [2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-(5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**68**, 0.220 g, 0.411 mmol) in 20.0 mL of 1,2-dichloroethane, triethylsilane (2.0 mL, 12 mmol) and trifluoroacetic acid (1.0 mL, 13 mmol) are added and the reaction stirred at 80 °C for 3 hours. The reaction is poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**P-3019**, 105.1 mg). MS (ESI) $[M+H^+]^+ = 364.2$.

[0684] [6-Fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine **P-4001** and [6-Fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine **P-4002**



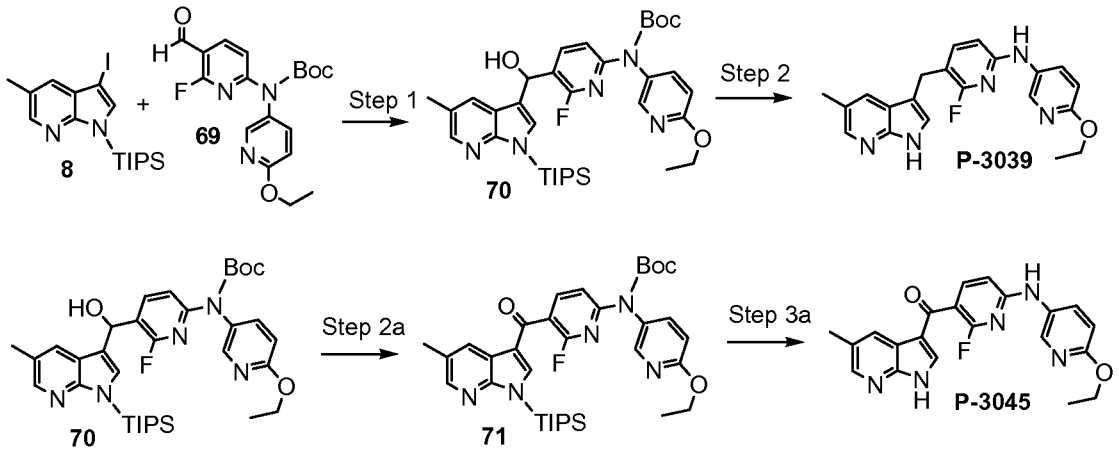
are prepared similarly to the protocol of Scheme 11, replacing 3-iodo-5-methyl-1-triisopropylsilanyl-

1H-pyrrolo[2,3-b]pyridine **8** with 5-iodo-4-methoxy-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidine **14** and 5-iodo-4-methyl-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidine **16**, respectively in step 1.

Example 12: Synthesis of (6-ethoxy-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-3039 or [6-(6-ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-3045.

[0685] (6-Ethoxy-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-3039** or [6-(6-ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-3045** are prepared in two steps or three steps from 3-iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **8**, and (6-ethoxy-pyridin-3-yl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **69** as shown in Scheme 12.

Scheme 12



Step 1 – Preparation of (6-Ethoxy-pyridin-3-yl)-{6-fluoro-5-[hydroxy-(5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl}-carbamic acid tert-butyl ester (70):

[0686] To a solution of 3-iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**8**, 0.43 g, 1.0 mmol) in 5 mL of tetrahydrofuran at -40 °C under nitrogen, isopropylmagnesium chloride (0.51 mL, 2.00 M in tetrahydrofuran, 1.0 mmol) is added slowly. The reaction is allowed to warm to -5 °C over 60 minutes, then cooled to -45 °C, followed by addition of (6-ethoxy-pyridin-3-yl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**69**, 0.06 g, 0.2 mmol) in 2.0 mL of tetrahydrofuran. The reaction is allowed to warm to room temperature over 2 hours, then poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**70**, 108.1 mg).

*Step 2 – Preparation of (6-ethoxy-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3039**):*

[0687] To (6-ethoxy-pyridin-3-yl)-{6-fluoro-5-[hydroxy-(5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl}-carbamic acid tert-butyl ester (**70**, 108.1 mg, 0.166 mmol) in 4.54 mL of 1,2-dichloroethane, triethylsilane (0.454 mL, 2.84 mmol) and trifluoroacetic acid (0.27 mL, 3.5 mmol) are added and the reaction stirred at 80 °C for 4 hours. The reaction is poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with 25-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**P-3039**), which is further purified by additional chromatography.

*Step 2a – Preparation of (6-ethoxy-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-carbamic acid tert-butyl ester (**71**):*

[0688] (6-Ethoxy-pyridin-3-yl)-{6-fluoro-5-[hydroxy-(5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl}-carbamic acid tert-butyl ester (**70**, 0.400 g, 0.616 mmol) is alternatively dissolved in 11.8 mL of dichloromethane, and Dess-Martin periodinane (0.100 g, 0.236 mmol) is added. The reaction is stirred at room temperature for 30 minutes, then concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fraction are combined and concentrated under vacuum to provide the desired compound (**71**, 0.200 g).

*Step 3a – Preparation of [6-(6-ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3045**):*

[0689] To (6-ethoxy-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-carbamic acid tert-butyl ester (**71**, 0.200 g, 0.309 mmol) in 10 mL of 1,2-dichloroethane, trifluoroacetic acid (0.80 mL, 10.0 mmol) is added. The reaction is stirred at 80 °C for 2 hours, then poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 2-15% methanol in dichloromethane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**P-3045**, 60.7 mg). MS (ESI) $[M+H^+]^+ = 391.9$.

[0690] Additional compounds are prepared following the protocol of Scheme 12. Compounds are made substituting either of 3-iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **8** with a suitable TIPS-protected 1H-pyrrolo[2,3-b]pyridine or 7H-pyrrolo[2,3-d]pyrimidine and (6-ethoxy-pyridin-3-yl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **69** with a suitable Boc-protected aldehyde in step 1. The following compounds are made using this procedure:

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-3019**),

[2-Fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3040**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-3041**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-3042**),

[2-Fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3043**),

(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-3044**),

(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-3048**),

[6-(6-Ethyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3049**),

(6-Chloro-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4003**),

(6-Ethoxy-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4005**),

(6-Ethoxy-pyridin-3-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4006**),

(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4007**),

(6-Ethyl-pyridin-3-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4009**),

[6-Fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-4010**),

(1-Ethyl-1H-pyrazol-4-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4011**),

[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(1-ethyl-1H-pyrazol-4-yl)-amine (**P-4012**),

(1-Ethyl-1H-pyrazol-4-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4013**),

[5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-4017**),

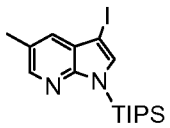
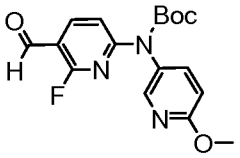
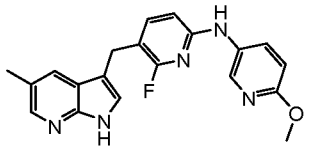
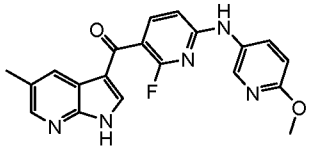
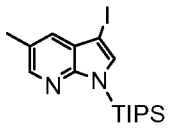
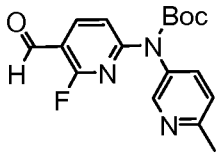
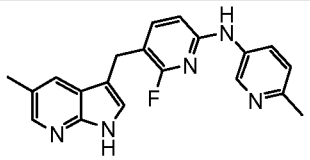
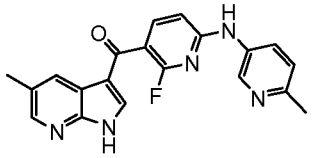
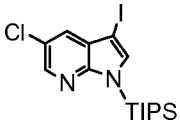
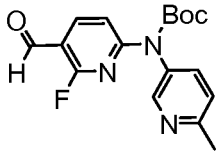
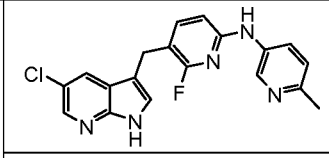
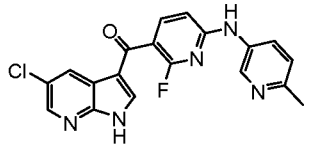
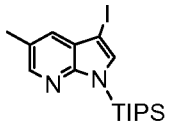
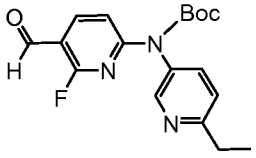
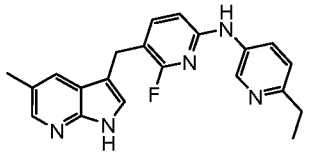
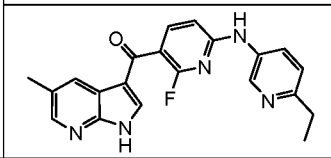
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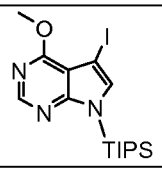
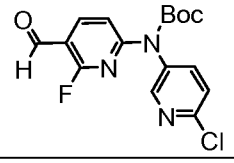
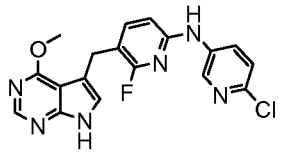
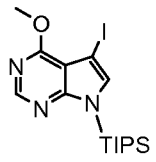
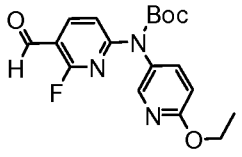
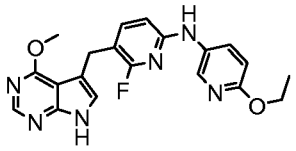
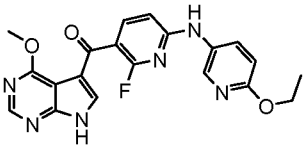
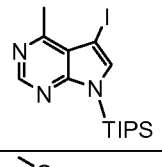
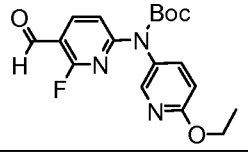
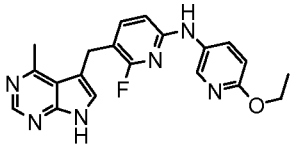
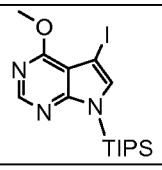
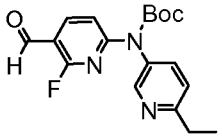
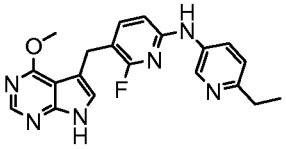
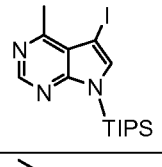
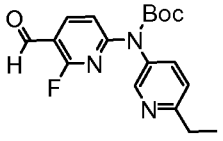
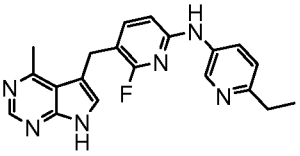
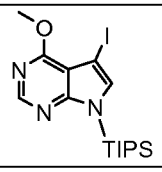
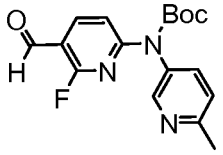
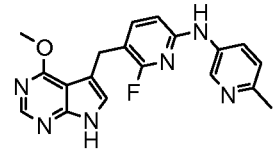
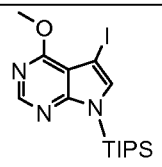
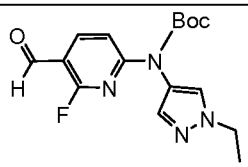
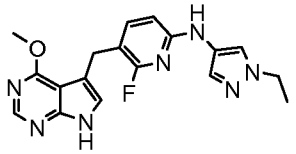
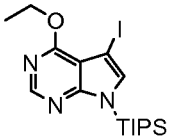
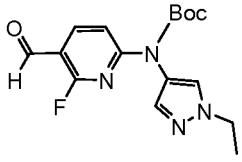
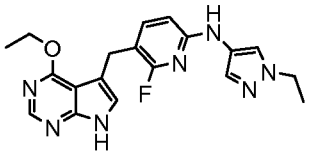
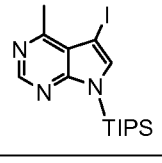
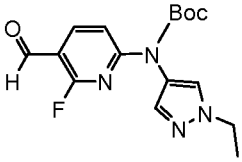
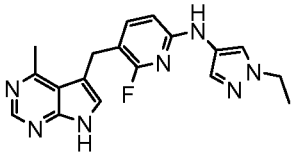
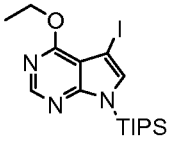
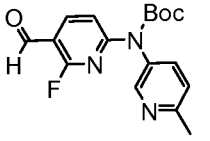
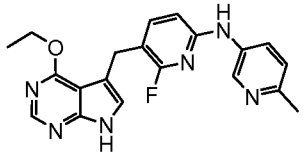
yl)-amine (**P-4018**),

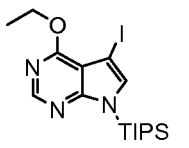
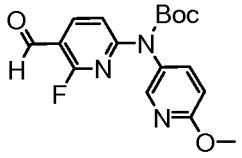
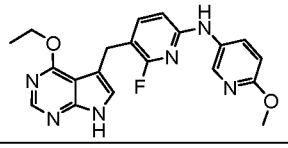
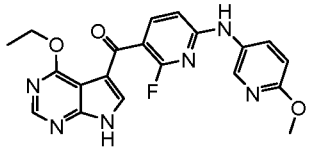
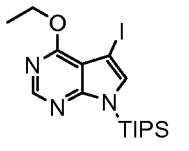
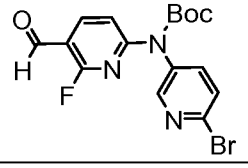
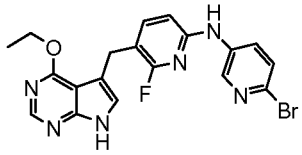
(6-Bromo-pyridin-3-yl)-[5-(4-ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-amine (**P-4020**),

The following table indicates the TIPS-protected 1H-pyrrolo[2,3-b]pyridine (column 2) and Boc-protected 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.

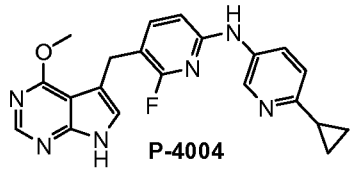
Table 5

Comp. number	pyrrolo[2,3-b]pyridine or pyrrolo[2,3-d]pyrimidine	Aldehyde	Compound structure	MS (ESI) $[M+H^+]^+$
P-3019				363.9
P-3040				378.0
P-3041				347.8
P-3043				361.9
P-3042				367.9
P-3044				382.0
P-3048				362.0
P-3049				376.1

P-4003				385.0
P-4005				394.95
P-4024				409.2
P-4006				378.95
P-4007				379.0
P-4009				
P-4010				365.0
P-4011				367.9
P-4012				382.1
P-4013				351.9
P-4017				379.0

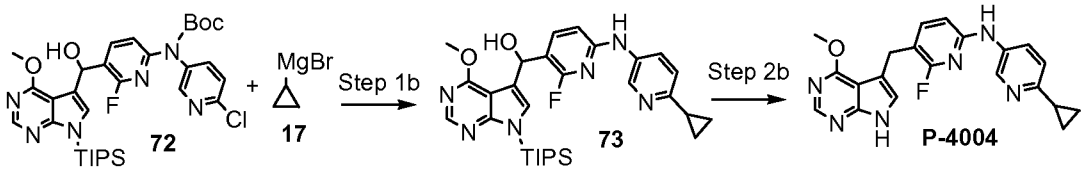
P-4018				394.8
P-4025				409.2
P-4020				442.9 444.9

[0691] (6-Cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine **P-4004**



P-4004

is prepared from the intermediate isolated after step 1 in the preparation of **P-4003** according to the following steps 1b and 2b.



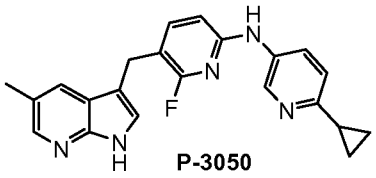
*Step 1b – Preparation of [6-(6-cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-methoxy-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanol (**73**):*

[0692] To (6-chloro-pyridin-3-yl)-{6-fluoro-5-[hydroxy-(4-methoxy-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methyl]-pyridin-2-yl}-carbamic acid tert-butyl ester (**72**, 105 mg, 0.160 mmol) in 3.8 mL of toluene, [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) 1:1 complex with dichloromethane (13.0 mg, 0.016 mmol) is added under an atmosphere of nitrogen. The reaction is stirred for 5 minutes, then cyclopropylmagnesium bromide (**17**, 1.60 mL, 1.0 M in tetrahydrofuran, 1.60 mmol) is added slowly. The reaction is heated at 65 °C for 5 hours, then poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**73**, 70 mg). MS (ESI) $[M+H^+]^+$ = 563.6.

*Step 2b – Preparation of (6-cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-4004**):*

[0693] To [6-(6-cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-methoxy-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanol (**73**, 70 mg, 0.12 mmol) in 10.0 mL of 1,2-dichloroethane, triethylsilane (1.00 mL, 6.26 mmol) and trifluoroacetic acid (0.60 mL, 7.8 mmol) are added and the reaction stirred at 80 °C for 4 hours. The reaction is poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**P-4004**, 11.8 mg). MS (ESI) $[M+H^+]^+ = 390.9$.

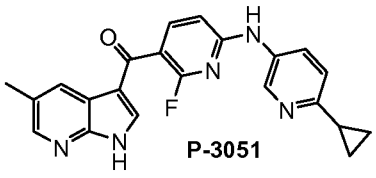
[0694] (6-Cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-3050**



P-3050

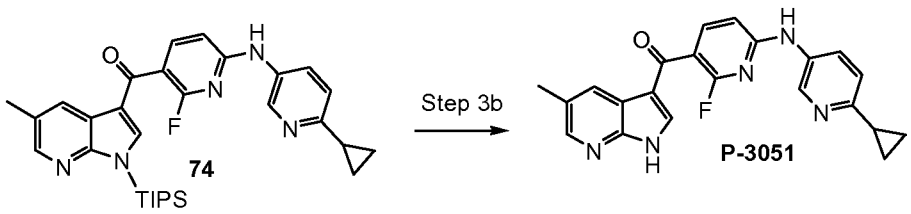
is prepared similarly to the protocol of Scheme 12, step 1, followed by steps 1b and 2b, where (6-ethoxy-pyridin-3-yl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **69** is replaced with (6-chloro-pyridin-3-yl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester in step 1. MS (ESI) $[M+H^+]^+ = 374.2$.

[0695] [6-(6-Cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-3051**



P-3051

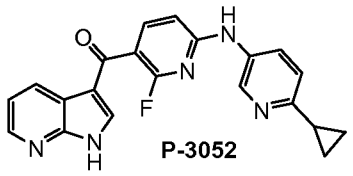
is similarly prepared from the intermediate formed from step 1b in the preparation of **P-3050**, reacting similarly to step 2a of Scheme 12, and then according to the following step 3b.



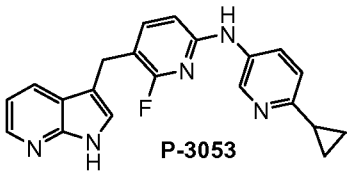
*Step 3b – Preparation of [6-(6-cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-3051**):*

[0696] To [6-(6-cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**74**, 134 mg, 0.25 mmol) in 10 mL of tetrahydrofuran, tetrabutylammonium fluoride, trihydrate (85.53 mg, 0.27 mmol) is added and the reaction stirred at room temperature for 30 minutes. Water is added and the mixture is extracted with ethyl acetate. The organic layer is washed with water and brine, 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 in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**P-3051**, 82 mg). MS (ESI) $[M+H^+]^+ = 388.0$.

[0697] [6-(6-Cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-3052** and (6-Cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-3053**



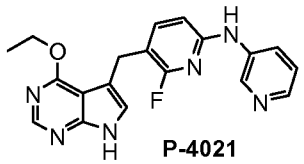
P-3052 and



P-3053

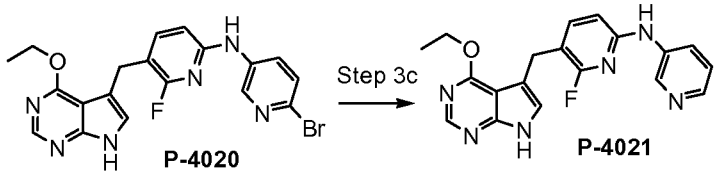
were prepared similarly to the protocols used for **P-3051** and **P-3052**, respectively, where 3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (prepared similarly to the protocol of Scheme 1, replacing 5-chloro-1H-pyrrolo[2,3-b]pyridine **1** with 1H-pyrrolo[2,3-b]pyridine in step 1) was used in place of 3-iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **8** in step 1. **P-3052** MS (ESI) $[M+H^+]^+ = 374.0$. **P-3053** MS (ESI) $[M+H^+]^+ = 359.9$.

[0698] [5-(4-Ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-pyridin-3-yl-amine **P-4021**



P-4021

is prepared from (6-bromo-pyridin-3-yl)-[5-(4-ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-amine **P-4020** according to the following step 3c.



P-4020 **P-4021**

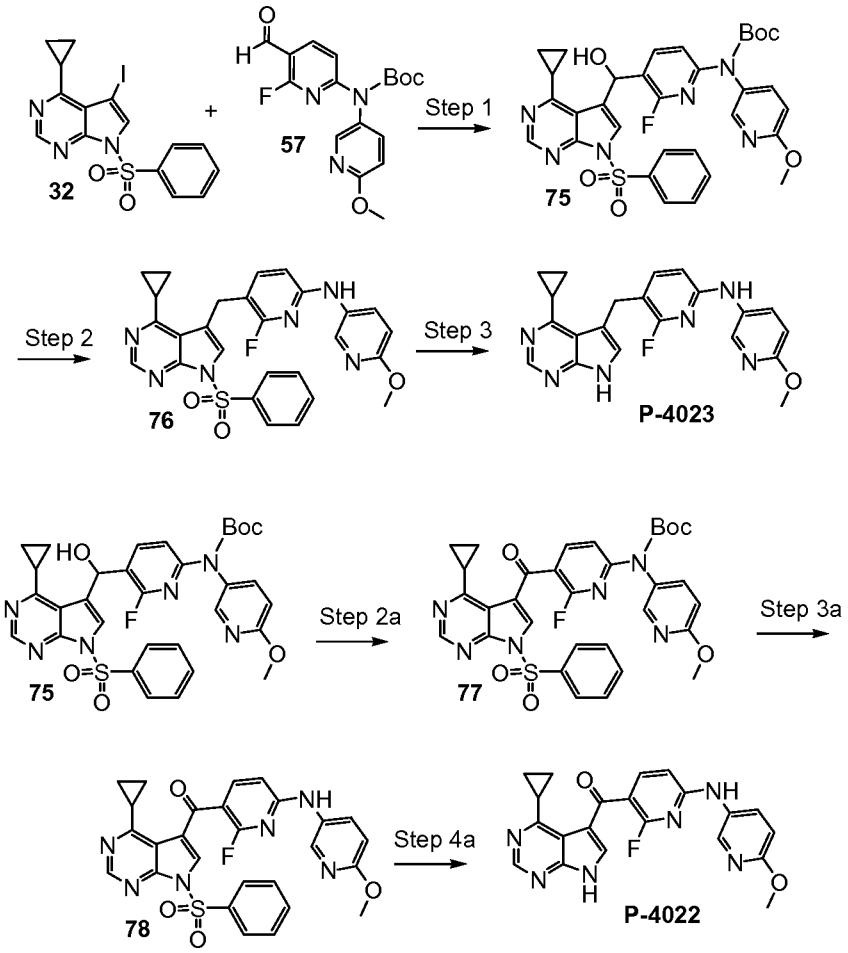
*Step 3b – Preparation of [5-(4-ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-pyridin-3-yl-amine (**P-4021**):*

[0699] To (6-bromo-pyridin-3-yl)-[5-(4-ethoxy-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-amine (**P-4020**, 0.040 g, 0.090 mmol) in 5.0 mL of tetrahydrofuran under nitrogen at -78 °C, tert-butyllithium (0.531 mL, 1.70 M in hexane, 0.903 mmol) is added. The reaction is stirred at -78 °C for 30 minutes, then poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified with silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**P-4021**, 25.7 mg). MS (ESI) $[M+H^+]^+ = 364.9$.

Example 13: Synthesis of [5-(4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine P-4023 or (4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-methanone P-4022.

[0700] [5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine **P-4023** or 4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-methanone **P-4022** are prepared in three steps or four steps from 7-benzenesulfonyl-4-cyclopropyl-5-iodo-7H-pyrrolo[2,3-d]pyrimidine **32** and (6-fluoro-5-formyl-pyridin-2-yl)-(6-methoxy-pyridin-3-yl)-carbamic acid tert-butyl ester **57** as shown in Scheme 13.

Scheme 13



*Step 1 – Preparation of {5-[(7-benzenesulfonyl-4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-hydroxy-methyl]-6-fluoro-pyridin-2-yl}-(6-methoxy-pyridin-3-yl)-carbamic acid tert-butyl ester (**75**):*

[0701] To a solution of 7-benzenesulfonyl-4-cyclopropyl-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (**32**, 0.760 g, 1.79 mmol) in 5.43 mL of tetrahydrofuran at -40 °C under nitrogen, isopropylmagnesium chloride (0.892 mL, 2.0 M in tetrahydrofuran, 1.78mmol) is added slowly. The reaction is allowed to warm to -5 °C over 75 minutes, then cooled to -45 °C and (6-fluoro-5-formyl-pyridin-2-yl)-(6-methoxy-pyridin-3-yl)-carbamic acid tert-butyl ester (**57**, 0.38 g, 1.1 mmol) in 2.0 mL of tetrahydrofuran is added. The reaction is allowed to warm to room temperature over 2 hours, then poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**75**, 0.64 g). MS (ESI) $[M+H^+]^+ = 647.2$.

*Step 2 – Preparation of [5-(7-Benzenesulfonyl-4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**76**):*

[0702] To {5-[(7-benzenesulfonyl-4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-hydroxy-methyl]-6-fluoro-pyridin-2-yl}-(6-methoxy-pyridin-3-yl)-carbamic acid tert-butyl ester (**75**, 0.290 g, 0.448 mmol) in 9.93 mL of 1,2-dichloroethane, triethylsilane (0.31 mL, 2.0 mmol) and trifluoroacetic acid (0.16 mL, 2.0 mmol) are added and the reaction stirred at 80 °C for 4 hours. The reaction is poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer is dried with sodium sulfate, filtered and the filtrate concentrated under vacuum to provide the desired compound (**76**, 170 mg). MS (ESI) $[M+H^+]^+ = 530.9$.

*Step 3 – Preparation of [5-(4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**P-4023**):*

[0703] To [5-(7-benzenesulfonyl-4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-amine (**76**, 0.170 g, 0.320 mmol) in 10.0 mL of tetrahydrofuran, tetrabutylammonium fluoride, trihydrate (0.174 g, 0.551 mmol) is added and the reaction is stirred at room temperature overnight. The reaction is poured into water and extracted with ethyl acetate. The organic layer is dried with sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**P-4023**, 100.4 mg). MS (ESI) $[M+H^+]^+ = 390.8$.

Step 2a – Preparation of [5-(7-benzenesulfonyl-4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-carbamic acid tert-butyl ester (77):

[0704] {5-[(7-Benzenesulfonyl-4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-hydroxy-methyl]-6-fluoro-pyridin-2-yl}-(6-methoxy-pyridin-3-yl)-carbamic acid tert-butyl ester (**75**, 0.350 g, 0.541 mmol) is alternatively dissolved in 10.0 mL of dichloromethane, and Dess-Martin periodinane (0.211 g, 0.498 mmol) is added. The reaction is stirred at room temperature for 30 minutes, then concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 10-100% ethyl acetate in hexane. Appropriate fraction are combined and concentrated under vacuum to provide the desired compound (**77**, 340 mg). MS (ESI) $[M+H^+]^+ = 645.4$.

*Step 3a – Preparation of (7-benzenesulfonyl-4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**78**):*

[0705] To [5-(7-benzenesulfonyl-4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-yl)-carbamic acid tert-butyl ester (**77**, 0.340 g, 0.527 mmol) in 10 mL of 1,2-dichloroethane, trifluorocetic acid (0.80 mL, 10.4 mmol) is added. The reaction is stirred at 80 °C for 45 minutes, then poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum to provide the desired compound (**78**, 235 mg). MS (ESI) $[M+H^+]^+ = 545.4$.

*Step 4a – Preparation of (4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-4022**):*

[0706] To (7-benzenesulfonyl-4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(6-methoxy-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**78**, 0.235 g, 0.432 mmol) in 10.0 mL of tetrahydrofuran, tetrabutylammonium fluoride, trihydrate (0.174 g, 0.551 mmol) is added. The reaction is stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fraction are combined and concentrated under vacuum to provide the desired compound (**P-4022**, 104.5 mg). MS (ESI) $[M+H^+]^+ = 405.0$.

[0707] Additional compounds are prepared following the protocol of Scheme 13. 4-Cyclopropyl-5-iodo-7-(toluene-4-sulfonyl)-7H-pyrrolo[2,3-d]pyrimidine **33** may be used in place of 7-benzenesulfonyl-4-cyclopropyl-5-iodo-7H-pyrrolo[2,3-d]pyrimidine **32**. Compounds are made substituting either of 7-benzenesulfonyl-4-cyclopropyl-5-iodo-7H-pyrrolo[2,3-d]pyrimidine **32** with a suitable benzenesulfonyl or 4-methybenzenesulfonyl-protected 7H-pyrrolo[2,3-d]pyrimidine or 1H-pyrrolo[2,3-b]pyridine and (6-ethoxy-pyridin-3-yl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **57** with a suitable Boc-protected aldehyde in step 1. In some instances, a non-Boc protected aldehyde is used as indicated in the following table (with no step 3a in this case). The following compounds are made using this procedure:

(6-Ethoxy-pyridin-3-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4008**),

(1-Ethyl-1H-pyrazol-4-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4014**),

{6-Fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-(6-methyl-pyridin-3-yl)-amine (**P-4015**),

(6-Ethyl-pyridin-3-yl)-{6-fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-amine (**P-4016**),

{6-Fluoro-5-[4-(2-methoxy-ethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl]-pyridin-2-yl}-(6-methoxy-pyridin-3-yl)-amine (**P-4019**),

[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-ethoxy-pyridin-3-yl)-amine (**P-4026**),

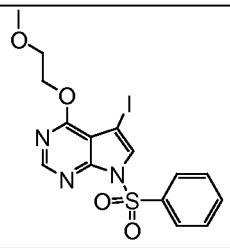
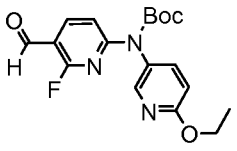
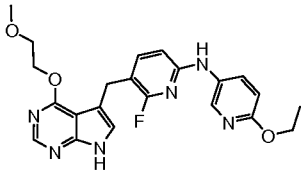
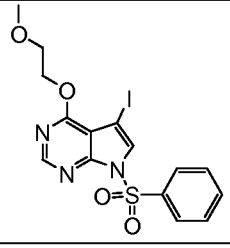
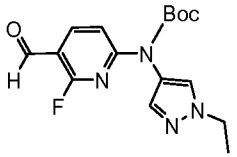
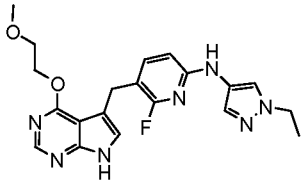
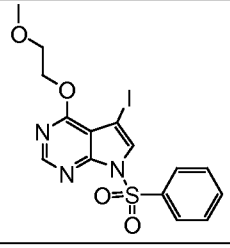
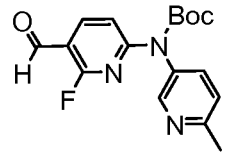
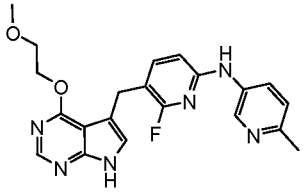
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-(6-ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-methanone (**P-4027**),

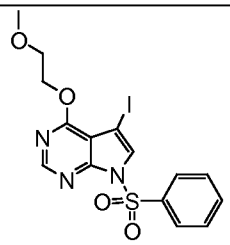
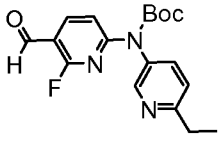
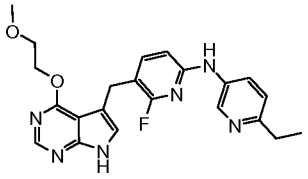
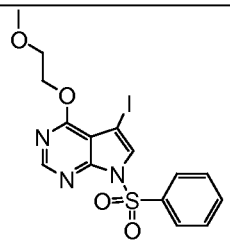
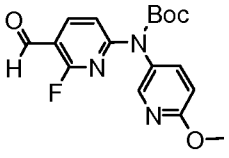
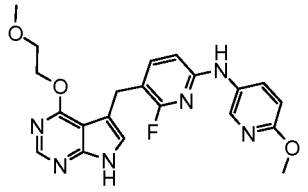
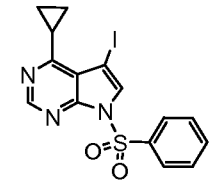
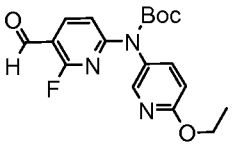
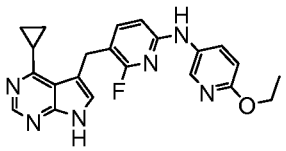
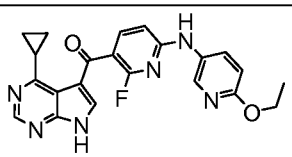
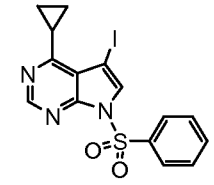
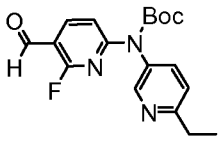
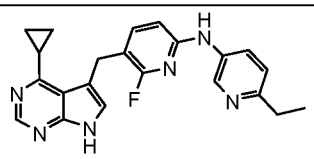
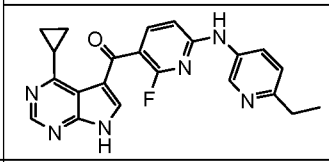
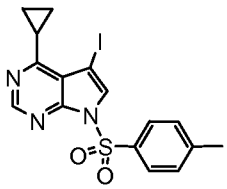
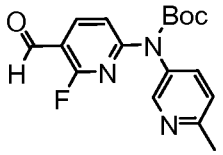
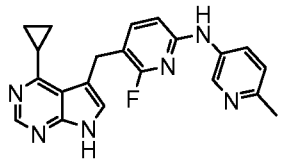
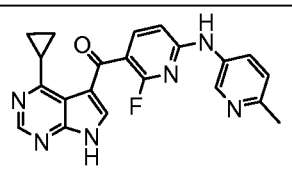
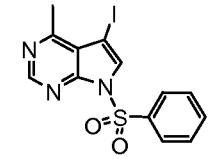
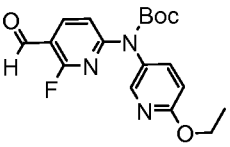
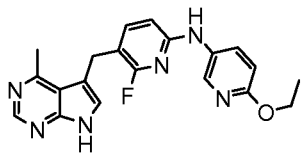
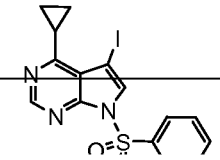
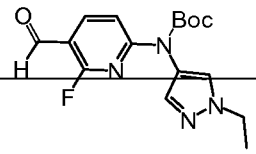
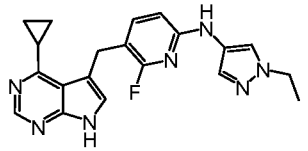
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-ethyl-pyridin-3-yl)-amine (**P-4028**),

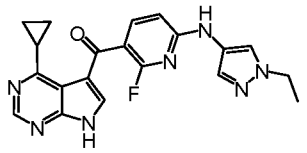
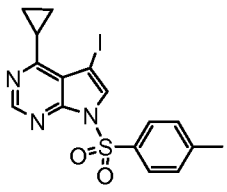
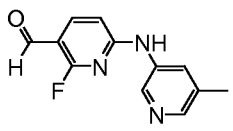
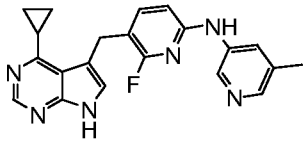
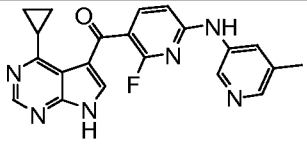
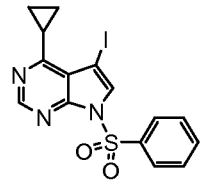
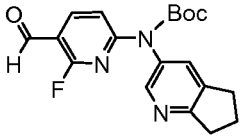
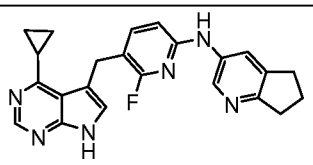
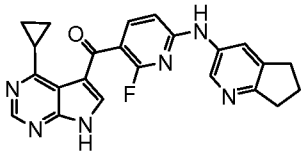
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-(6-ethyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-

yl]-methanone (**P-4029**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methyl-pyridin-3-yl)-amine (**P-4030**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(6-methyl-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-4031**),
[6-(6-Ethoxy-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**P-4032**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(1-ethyl-1H-pyrazol-4-yl)-amine (**P-4036**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[6-(1-ethyl-1H-pyrazol-4-ylamino)-2-fluoro-pyridin-3-yl]-methanone (**P-4037**),
[5-(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-methyl-pyridin-3-yl)-amine (**P-4038**),
(4-Cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-[2-fluoro-6-(5-methyl-pyridin-3-ylamino)-pyridin-3-yl]-methanone (**P-4039**),
The following table indicates the Benzenesulfonyl-protected 1H-pyrrolo[2,3-b]pyridine (column 2) and Boc-protected 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.

Table 6

Comp. number	pyrrolo[2,3-b]pyridine	Aldehyde	Compound structure	MS (ESI) $[M+H^+]^+$
P-4008				439.0
P-4014				412.0
P-4015				409.0

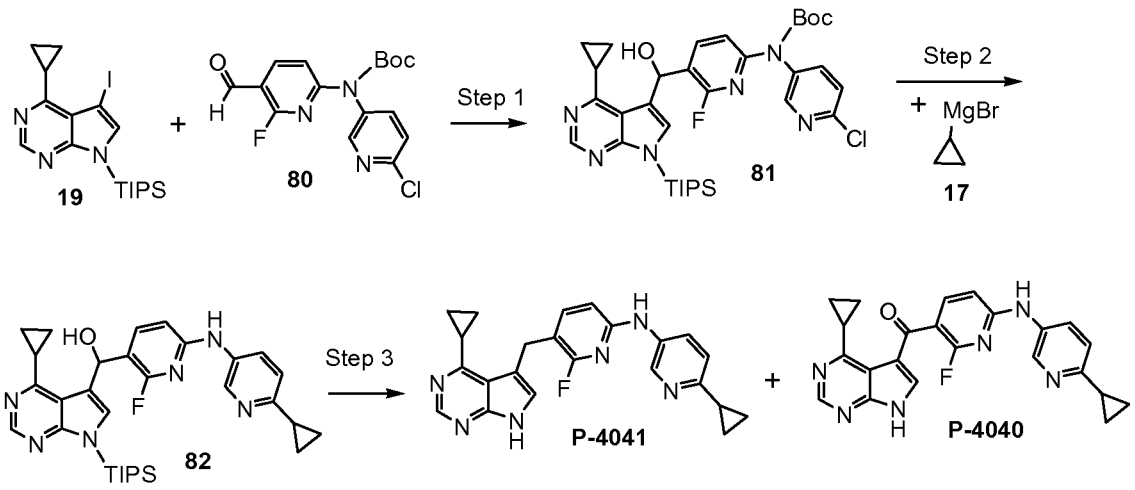
P-4016				423.0
P-4019				424.9
P-4026				404.9
P-4027				418.8
P-4028				389.0
P-4029				402.9
P-4030				375.0
P-4031				388.9
P-4032				393.1
P-4036				378.0

P-4037				392.0
P-4038				375.1
P-4039				389.1
P-4042				
P-4043				

Example 14: Synthesis of [6-(6-cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone P-4040 and (6-cyclopropyl-pyridin-3-yl)-[5-(4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-amine P-4041.

[0708] [6-(6-Cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone **P-4040** and (6-cyclopropyl-pyridin-3-yl)-[5-(4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-amine **P-4041** are prepared in three steps from 4-cyclopropyl-5-iodo-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidine **19** and (6-chloro-pyridin-3-yl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **80** as shown in Scheme 14.

Scheme 14



*Step 1 – Preparation of (6-chloro-pyridin-3-yl)-{5-[(4-cyclopropyl-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-hydroxy-methyl]-6-fluoro-pyridin-2-yl}-carbamic acid tert-butyl ester (**81**):*

[0709] To 4-cyclopropyl-5-iodo-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidine (**19**, 0.72 g, 1.64 mmol) in 6.0 mL of tetrahydrofuran at -40 °C under nitrogen, isopropylmagnesium chloride (0.82 mL, 2.01 M in tetrahydrofuran, 1.65 mmol) is added slowly. The reaction is allowed to warm to -5 °C in 75 minutes, then cooled to -45 °C and (6-chloro-pyridin-3-yl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**80**, 0.48 g, 1.38 mmol) in 5.0 mL is added. The reaction is allowed to warm to room temperature in 2 hours, then poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**81**, 0.51 g). MS (ESI) $[M+H^+]^+ = 667.2$).

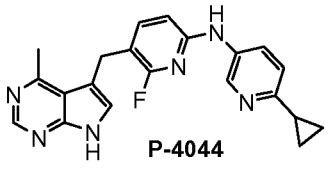
*Step 2 – Preparation of [6-(6-cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-cyclopropyl-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanol (**82**):*

[0710] To (6-chloro-pyridin-3-yl)-{5-[(4-cyclopropyl-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-hydroxy-methyl]-6-fluoro-pyridin-2-yl}-carbamic acid tert-butyl ester (**81**, 0.51 g, 0.77 mmol) in 12 mL of toluene, [1,1'-bis(diphenylphosphino) ferrocene]dichloropalladium(II) (0.13 g, 0.17 mmol) is added under nitrogen and the reaction stirred for 5 minutes. Cyclopropylmagnesium bromide (**17**, 15.29 mL, 0.50 M in tetrahydrofuran, 7.65 mmol) is added slowly and the reaction is heated at 65 °C for 2 hours. The reaction is poured into water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound (**82**, 400 mg).

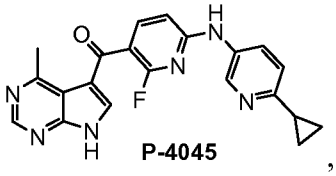
*Step 3 – Preparation of [6-(6-cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**P-4040**) and (6-cyclopropyl-pyridin-3-yl)-[5-(4-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-6-fluoro-pyridin-2-yl]-amine (**P-4041**):*

[0711] To [6-(6-cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-cyclopropyl-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanol (**82**, 400 mg, 0.7 mmol) in 30 mL of dichloromethane, triethylsilane (2.6 mL, 16.28 mmol) and trifluoroacetic acid (1.5 mL, 15.13 mmol) are added, and the reaction is stirred at 80 °C for 3 hours. The reaction is poured into aqueous potassium carbonate 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 purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane to give a mixture of compounds **P-4040** and **P-4041**. These are separated by preparative HPLC to provide the isolated compounds (**P-4040**, 3.0 mg, MS (ESI) $[M+H^+]^+ = 414.9$), (**P-4041**, 37.9 mg, MS (ESI) $[M+H^+]^+ = 401.0$).

[0712] (6-Cyclopropyl-pyridin-3-yl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine **P-4044** and [6-(6-cyclopropyl-pyridin-3-ylamino)-2-fluoro-pyridin-3-yl]-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone **P-4045**


P-4044

and

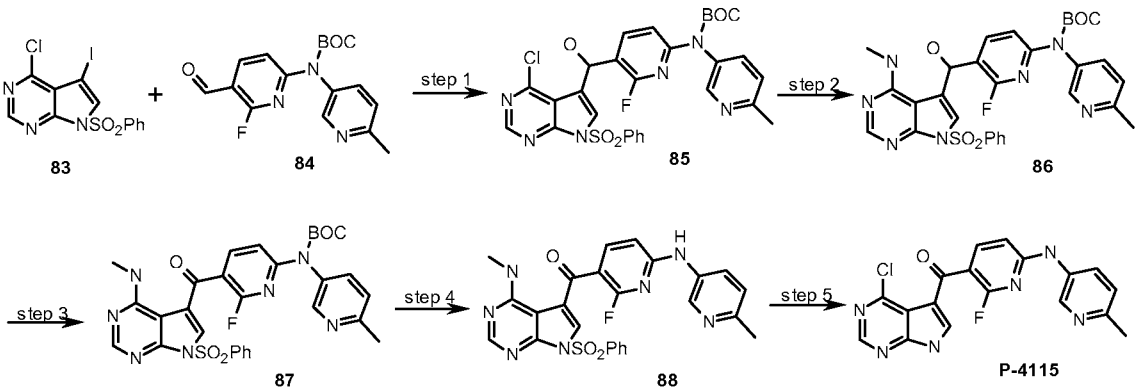

P-4045

,

are prepared similarly to Scheme 14, where 4-cyclopropyl-5-iodo-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidine **19**, is replaced in step 1 with 5-iodo-4-methyl-7H-pyrrolo[2,3-d]pyrimidine (prepared similarly to Scheme 4 steps 1 and 2). **P-4044**, 2.5 mg, MS (ESI) $[M+H^+]^+$ 375.0. **P-4045**, 5.3 mg, MS (ESI) $[M+H^+]^+ = 388.9$.

Example 15: Synthesis of [2-fluoro-6-[(6-methyl-3-pyridyl)amino]-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (P-4115)

Scheme 15



*Step 1- Preparation of tert-butyl N-[5-[[7-(benzenesulfonyl)-4-chloro-pyrrolo[2,3-d]pyrimidin-5-yl]-hydroxy-methyl]-6-fluoro-2-pyridyl]-N-(6-methyl-3-pyridyl)carbamate **85***

[0713] To a solution of 7-(benzenesulfonyl)-4-chloro-5-iodo-pyrrolo[2,3-d]pyrimidine (**1**, 0.43 g, 1.01 mmol) in Tetrahydrofuran (5 mL) at -30 °C under nitrogen was added 2.0 M Isopropylmagnesium Chloride in Tetrahydrofuran (0.5 ml) slowly. The reaction was allowed to warm to -5 °C in 75 minutes. Then, the reaction was cooled to -45 °C, followed by adding tert-butyl N-(6-fluoro-5-formyl-2-pyridyl)-N-(6-methyl-3-pyridyl)carbamate (**84**, 0.24 g, 0.72 mmol) in THF (3.0 mL). The reaction was allowed to warm to room temperature in around 2 hours. The reaction was poured in to water, extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, purified with silica gel column chromatography eluting with 20%-100% ethyl acetate in hexane to give product (85, 0.41 g, 90.6%). MS (ESI) [M+H+]+ = 625.0.

*Step 2- Preparation of tert-butyl N-[5-[[7-(benzenesulfonyl)-4-methylamino-pyrrolo[2,3-d]pyrimidin-5-yl]-hydroxy-methyl]-6-fluoro-2-pyridyl]-N-(6-methyl-3-pyridyl)carbamate **86***

[0714] To tert-butyl N-[5-[[7-(benzenesulfonyl)-4-chloro-pyrrolo[2,3-d]pyrimidin-5-yl]-hydroxy-methyl]-6-fluoro-2-pyridyl]-N-(6-methyl-3-pyridyl)carbamate (**85**, 75 mg, 0.12 mmol) in Isopropyl alcohol (0.80 mL) was added 2M methylamine in THF (0.6 ml). The resulting solution was stirred at 40 °C for 6 hours. The reaction was concentrated to give product (86, 70 mg, 94.2%). MS (ESI) [M+H+]+ = 620.

*Step 3–Preparation of tert-butyl N-[5-[7-(benzenesulfonyl)-4-methylamino-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-6-fluoro-2-pyridyl]-N-(6-methyl-3-pyridyl)carbamate **87***

[0715] To tert-butyl N-[5-[[7-(benzenesulfonyl)-4-methylamino-pyrrolo[2,3-d]pyrimidin-5-yl]-hydroxy-methyl]-6-fluoro-2-pyridyl]-N-(6-methyl-3-pyridyl)carbamate (**86**, 0.07 g, 0.11 mmol) in DCM (10 mL) was added DMP (0.06 g, 0.14 mmol). The reaction was stirred at room temperature for 20 minutes. The reaction was concentrated, and purified with silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give product (**87**, 0.065 g, 93.6%).

*Step 4 – Preparation of [7-(benzenesulfonyl)-4-methylamino-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(6-methyl-3-pyridyl)amino]-3-pyridyl]methanone; 2,2,2-trifluoroacetic acid **88***

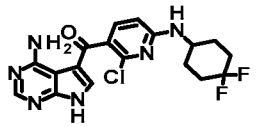
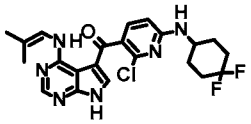
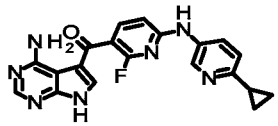
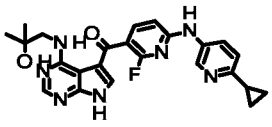
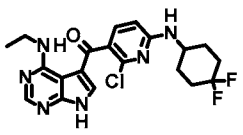
[0716] To tert-butyl N-[5-[7-(benzenesulfonyl)-4-methylamino-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-6-fluoro-2-pyridyl]-N-(6-methyl-3-pyridyl)carbamate (**87**, 65 mg, 0.11 mmol) in dichloroethane (10 mL) was added TFA (0.65 ml, 8.75 mmol). The reaction was heated 80 °C for 1 hour. The reaction was concentrated to give crude product (CF3COOH salt) around (**88**, 0.080 g, 86.4%). MS (ESI) [M+H+]+ = 518. MS is the free base product.

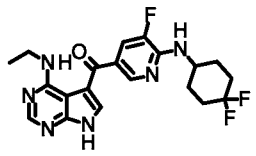
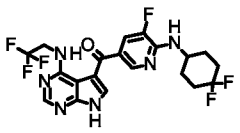
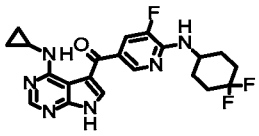
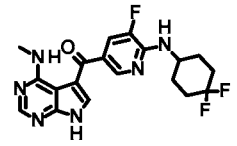
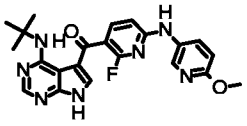
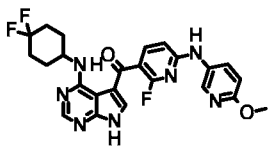
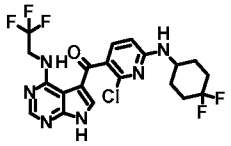
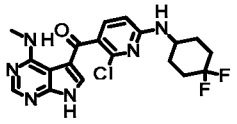
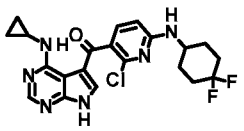
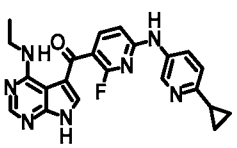
Step 5 – Preparation of [2-fluoro-6-[(6-methyl-3-pyridyl)amino]-3-pyridyl]-(4-methylamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone ***P-4115***

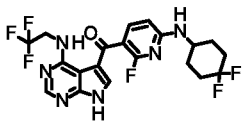
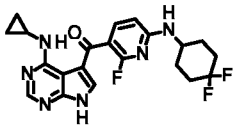
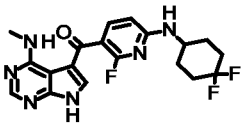
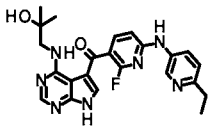
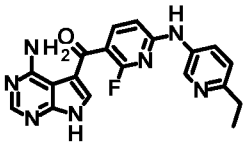
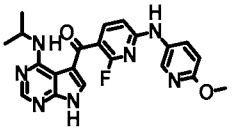
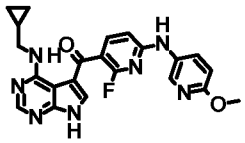
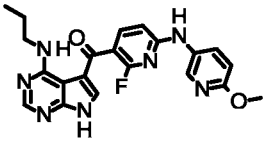
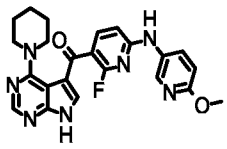
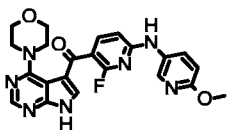
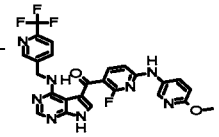
[0717] To [7-(benzenesulfonyl)-4-methylamino-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(6-methyl-3-pyridyl)amino]-3-pyridyl]methanone; 2,2,2-trifluoroacetic acid (**88**, 80 mg, 0.09 mmol) in Methanol (6 ml) was added KOH (0.1 g, 1.78 mmol). The reaction was stirred at room temperature for 1 hour. The reaction mixture was concentrated and purified with silica gel column chromatography eluting with 2% to 25% methanol in methylene chloride to give product (**P-4115**, 9.6 mg, 27.3%). MS (ESI) [M+H+]+ = 377.9.

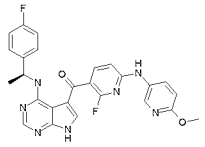
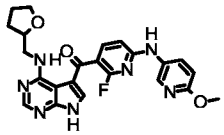
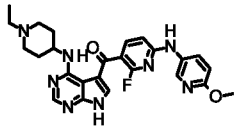
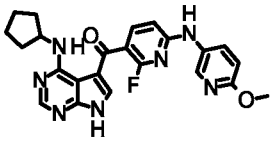
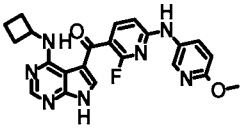
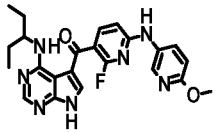
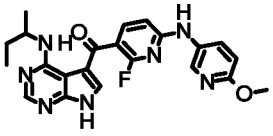
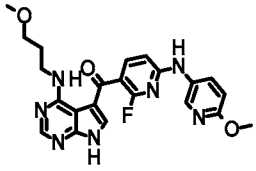
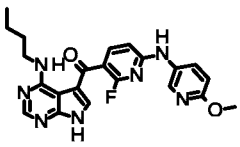
Table 2 below provides compounds prepared according to the synthetic protocols set forth in Schemes 14 and 15. The structures were characterized by mass spectroscopy and ^{1}H and ^{13}C NMR spectroscopies.

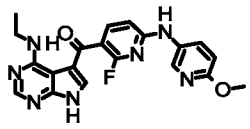
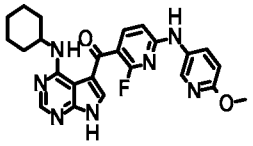
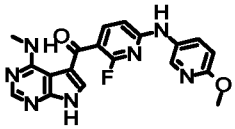
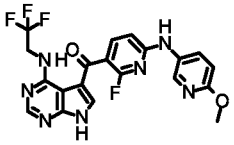
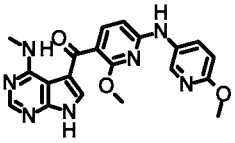
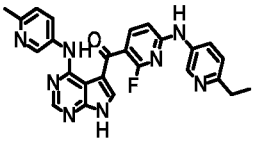
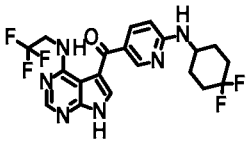
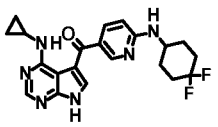
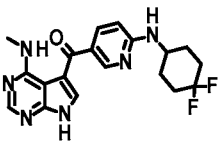
Table 2

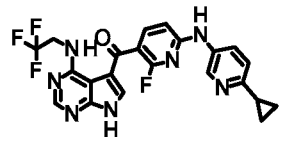
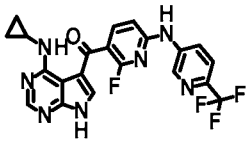
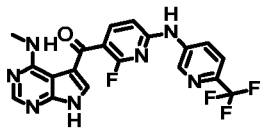
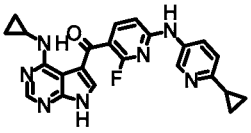
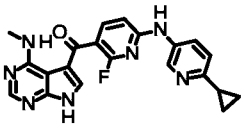
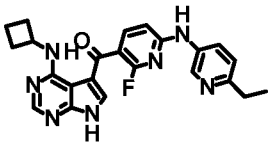
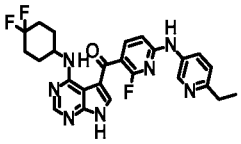
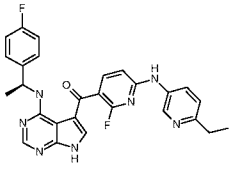
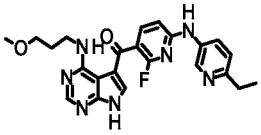
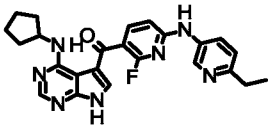
No.	Compound Structure	MS (ESI) $[M+H^+]^+$
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P-4047		461.3
P-4048		390.1
P-4049		462.1
P-4050		435.0

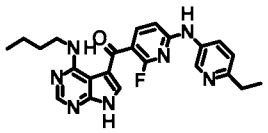
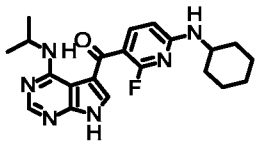
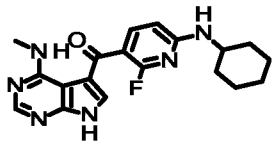
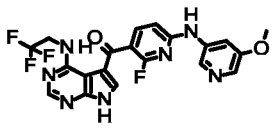
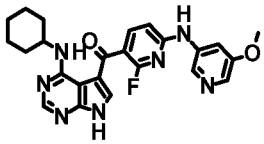
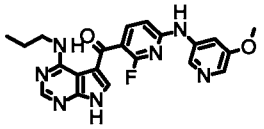
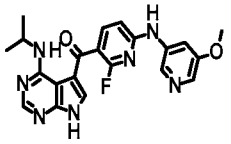
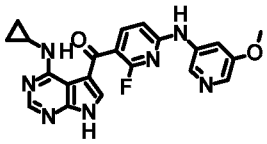
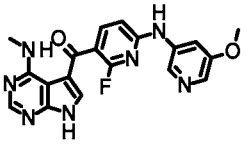
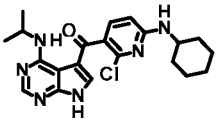
No.	Compound Structure	MS (ESI) $[M+H^+]^+$
P-4051		419.0
P-4052		472.95
P-4053		431.0
P-4054		405.0
P-4055		436.5
P-4056		498.5
P-4057		489.0
P-4058		420.9
P-4059		447.1
P-4060		418.0

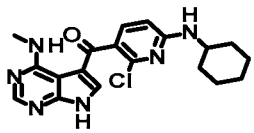
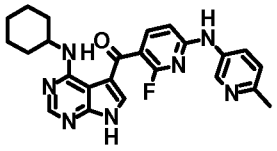
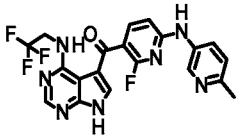
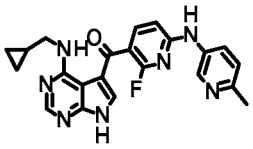
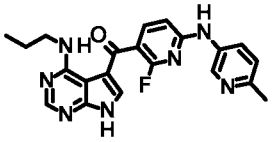
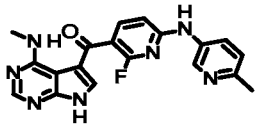
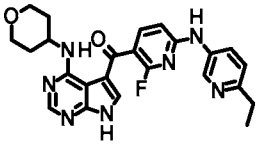
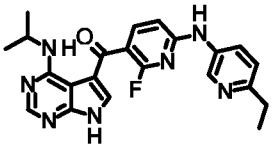
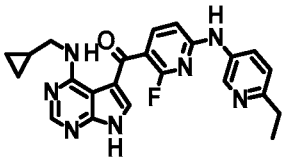
No.	Compound Structure	MS (ESI) $[M+H^+]^+$
P-4061		473.0
P-4062		431.1
P-4063		405.0
P-4064		445.0
P-4065		377.9
P-4066		422.0
P-4067		434.5
P-4068		422.0
P-4069		449.5
P-4070		450.0
P-4071		539.5

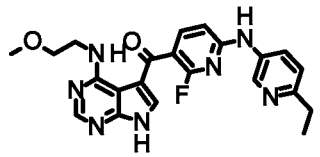
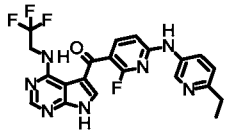
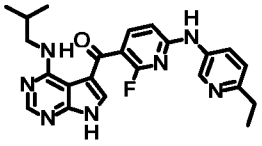
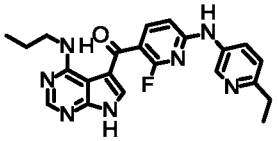
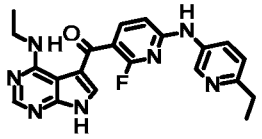
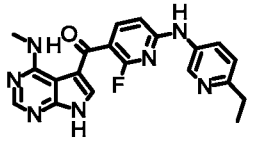
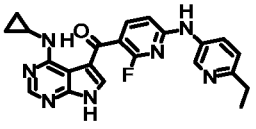
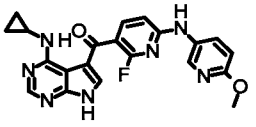
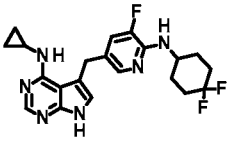
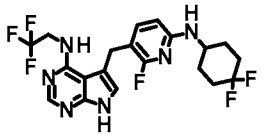
No.	Compound Structure	MS (ESI) $[M+H^+]^+$
P-4072		502.5
P-4073		464.0
P-4074		491.5
P-4075		448.0
P-4076		434.5
P-4077		450.0
P-4078		436.5
P-4079		452.0
P-4080		436.5

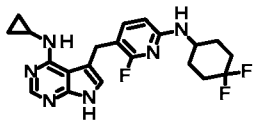
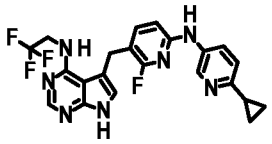
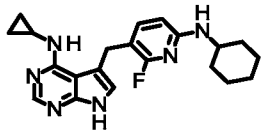
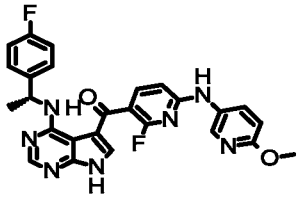
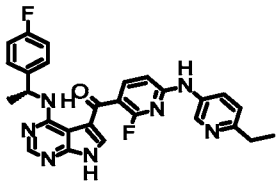
No.	Compound Structure	MS (ESI) $[M+H^+]^+$
P-4081		408.5
P-4082		462.5
P-4083		394.5
P-4084		462.5
P-4085		406.0
P-4086		469.5
P-4087		455.2
P-4088		413.2
P-4089		387.2

No.	Compound Structure	MS (ESI) $[M+H^+]^+$
P-4090		470.2
P-4091		458.0
P-4092		432.0
P-4093		429.9
P-4094		403.9
P-4095		432.5
P-4096		496.5
P-4097		500.5
P-4098		450.0
P-4099		446.5

No.	Compound Structure	MS (ESI) $[M+H^+]^+$
P-4100		434.5
P-4101		397.5
P-4102		369.1
P-4103		462.1
P-4104		462.1
P-4105		422.0
P-4106		422.2
P-4107		420.2
P-4108		393.9
P-4109		412.9

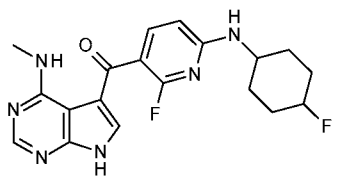
No.	Compound Structure	MS (ESI) $[M+H^+]^+$
P-4110		384.9
P-4111		446.1
P-4112		446.0
P-4113		418.1
P-4114		406.0
P-4115		377.9
P-4116		462.1
P-4117		420.0
P-4118		432.2

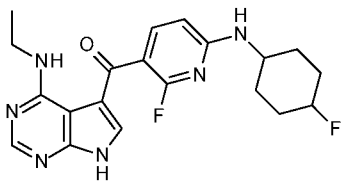
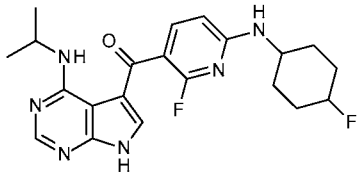
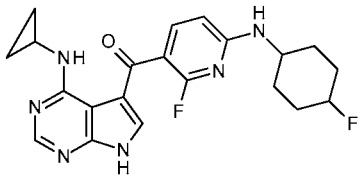
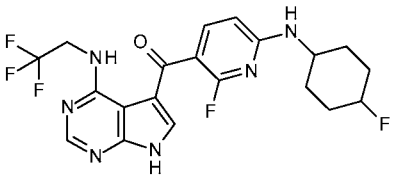
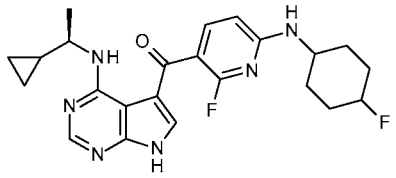
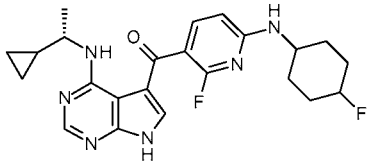
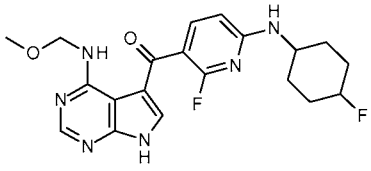
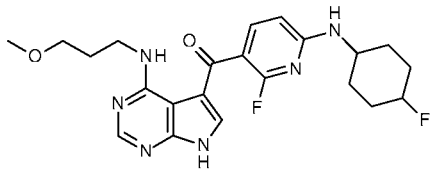
No.	Compound Structure	MS (ESI) $[M+H^+]^+$
P-4119		436.1
P-4120		460.1
P-4121		434.1
P-4122		420.0
P-4123		406.5
P-4124		391.9
P-4125		418.0
P-4126		420.0
P-4127		417.0
P-4128		459.0

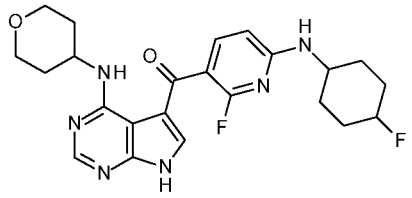
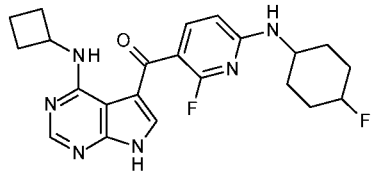
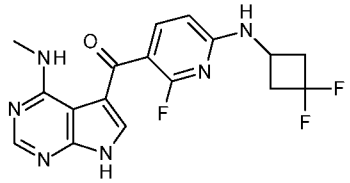
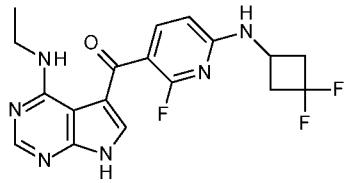
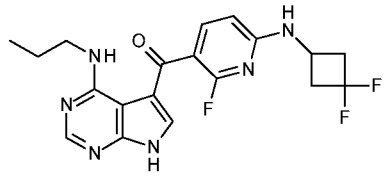
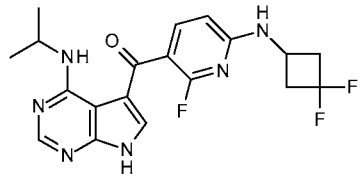
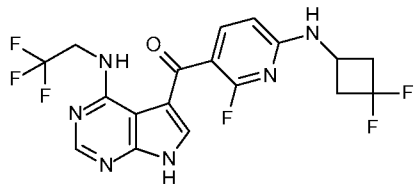
No.	Compound Structure	MS (ESI) $[M+H^+]^+$
P-4129		417.0
P-4130		458.0
P-4131		379.0
P-4132		502.5
P-4133		500.5

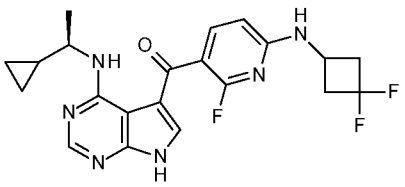
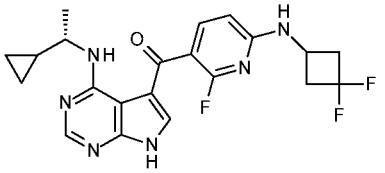
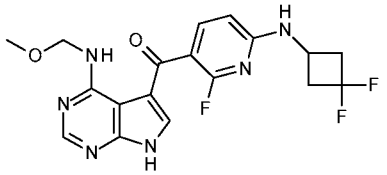
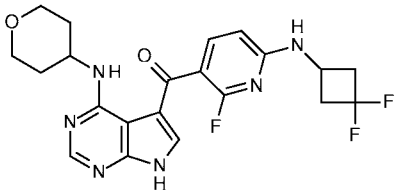
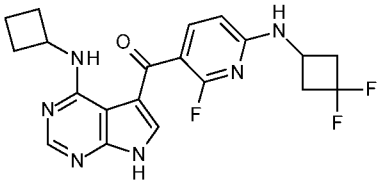
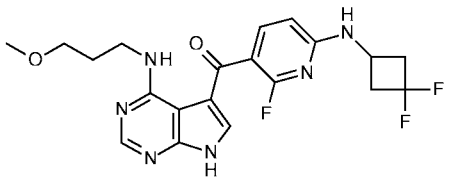
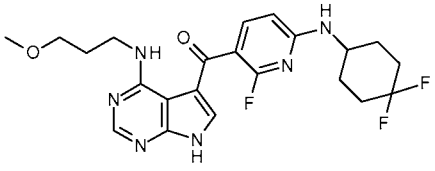
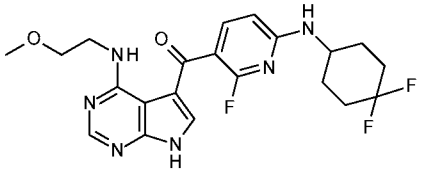
The compounds set forth in Table 7 below are prepared according to the synthetic protocols set forth in Schemes 14 and 15. The structures are characterized by mass spectroscopy and ^{1}H and ^{13}C NMR spectroscopies.

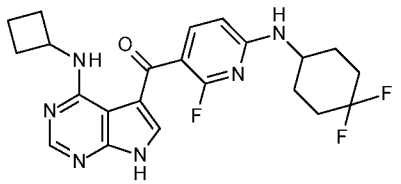
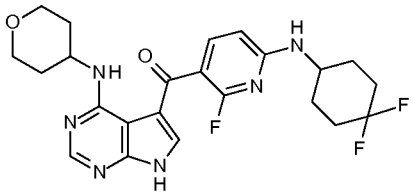
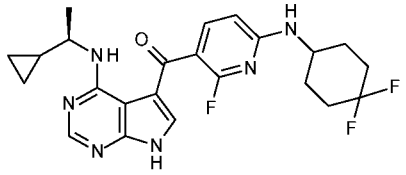
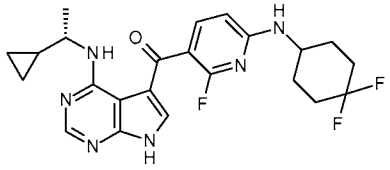
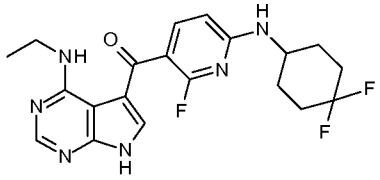
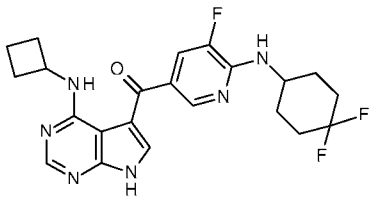
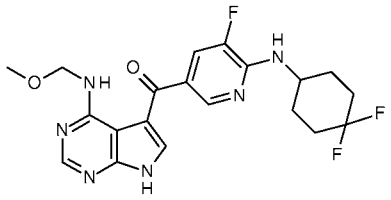
Table 7

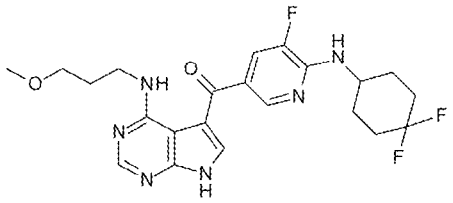
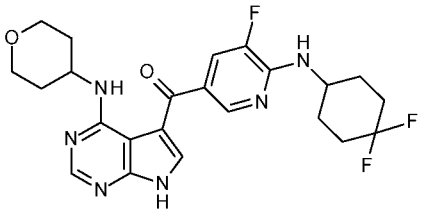
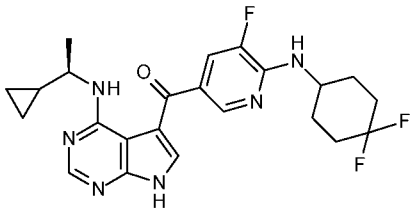
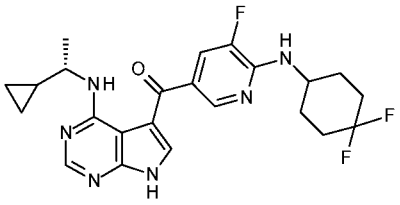
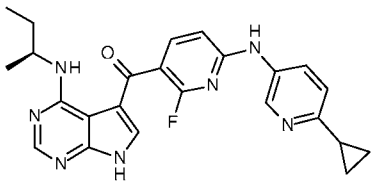
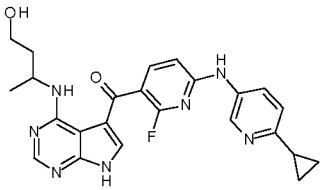
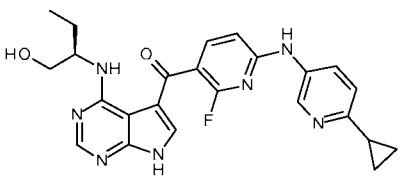
No	Name	Structure
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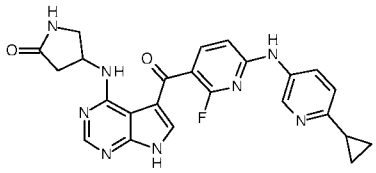
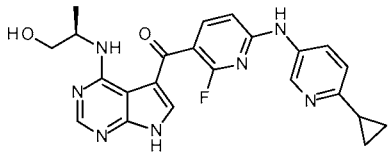
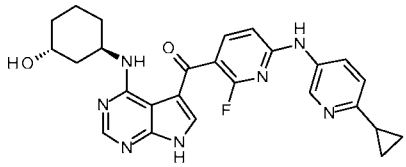
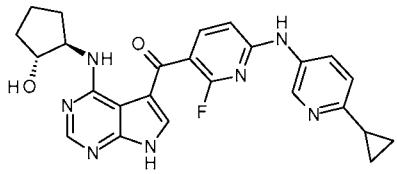
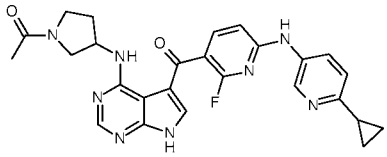
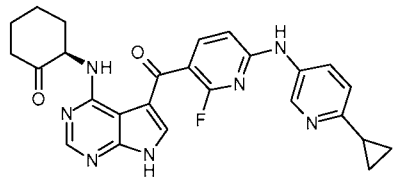
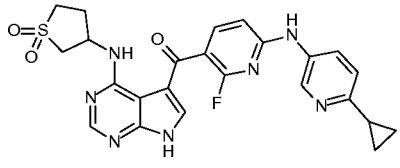
No	Name	Structure
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P-4136	[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]-[4-(isopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4137	[4-(cyclopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]methanone	
P-4138	[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]-[4-(2,2,2-trifluoroethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4139	[4-[[(1R)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]methanone	
P-4140	[4-[[(1S)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]methanone	
P-4141	[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]-[4-(methoxymethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4142	[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]-[4-(3-methoxypropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-	

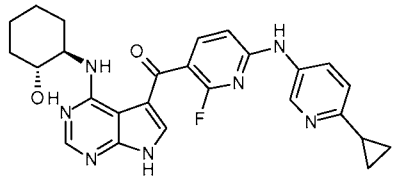
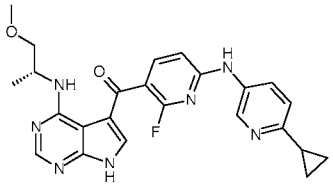
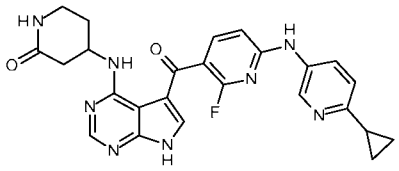
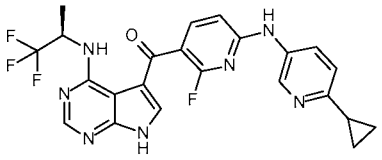
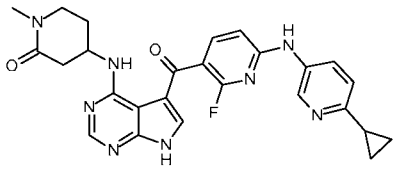
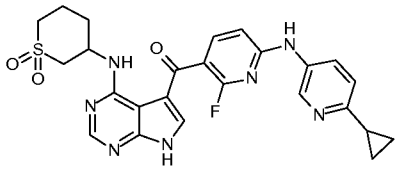
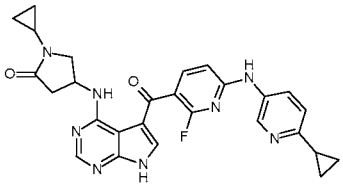
No	Name	Structure
	yl]methanone	
P-4143	[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]-[4-(tetrahydropyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4144	[4-(cyclobutylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[2-fluoro-6-[(4-fluorocyclohexyl)amino]-3-pyridyl]methanone	
P-4145	[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4146	[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4147	[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(propylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4148	[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(isopropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4149	[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(2,2,2-trifluoroethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	

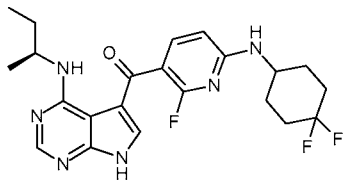
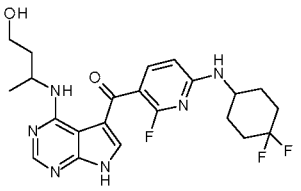
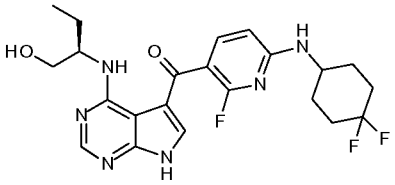
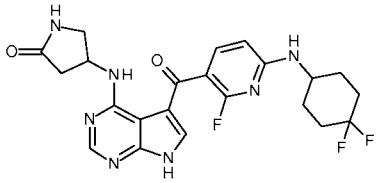
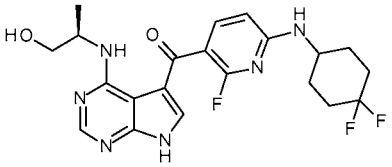
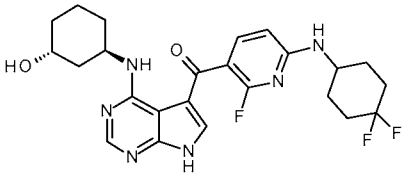
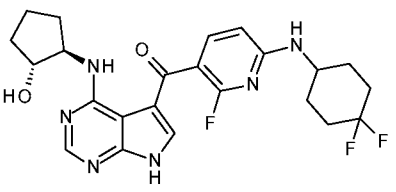
No	Name	Structure
P-4150	[4-[[(1R)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]methanone	
P-4151	[4-[[(1S)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]methanone	
P-4152	[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(methoxymethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4153	[6-[(3,3-15difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(tetrahydropyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4154	[4-(cyclobutylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]methanone	
P-4155	[6-[(3,3-difluorocyclobutyl)amino]-2-fluoro-3-pyridyl]-[4-(3-methoxypropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4156	[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-(3-methoxypropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4157	[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-(2-methoxyethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	

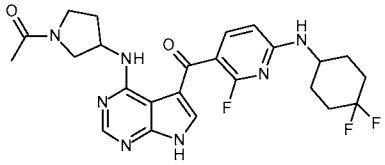
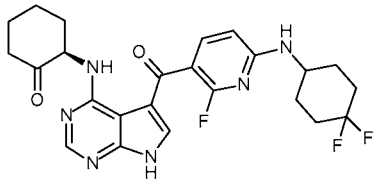
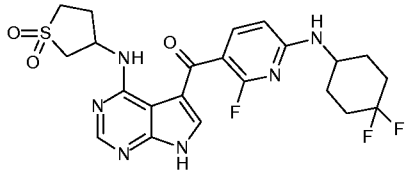
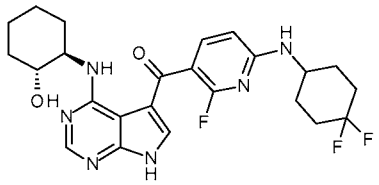
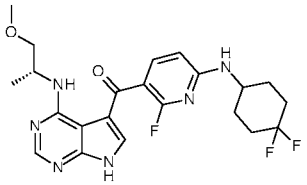
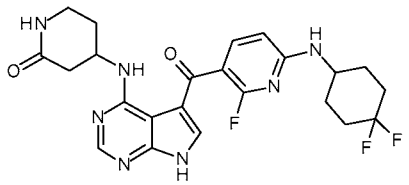
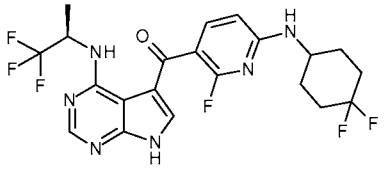
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P-4158	[4-(cyclobutylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]methanone	
P-4159	[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-(tetrahydropyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4160	[4-[[(1R)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]methanone	
P-4161	[4-[[(1S)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]methanone	
P-4162	[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-(ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4163	[4-(cyclobutylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]methanone	
P-4164	[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]-[4-(methoxymethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	

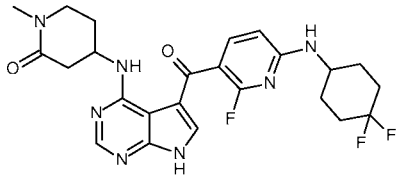
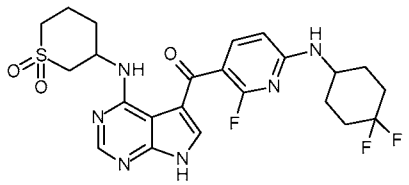
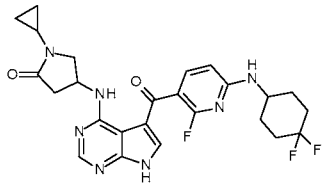
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P-4165	[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]-[4-(3-methoxypropylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4166	[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]-[4-(tetrahydropyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4167	[4-[[(1R)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]methanone	
P-4168	[4-[[(1S)-1-cyclopropylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-[6-[(4,4-difluorocyclohexyl)amino]-5-fluoro-3-pyridyl]methanone	
P-4169	[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1S)-1-methylpropyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4170	[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[(3-hydroxy-1-methyl-propyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4171	[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-1-(hydroxymethyl)propyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	

No	Name	Structure
P-4172	4-[[5-[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]pyrrolidin-2-one	
P-4173	[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-2-hydroxy-1-methyl-ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4174	[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R,3R)-3-hydroxycyclohexyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4175	[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R,2R)-2-hydroxycyclopentyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4176	1-[3-[[5-[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]pyrrolidin-1-yl]ethanone	
P-4177	(2R)-2-[[5-[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]cyclohexanone	
P-4178	[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[(1,1-dioxothiolan-3-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	

No	Name	Structure
P-4179	[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R,2R)-2-hydroxycyclohexyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4180	[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-2-methoxy-1-methyl-ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4181	4-[[5-[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]piperidin-2-one	
P-4182	[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-2,2,2-trifluoro-1-methyl-ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4183	4-[[5-[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-methyl-piperidin-2-one	
P-4184	[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-3-pyridyl]-[4-[(1,1-dioxothian-3-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4185	1-cyclopropyl-4-[[5-[6-[(6-cyclopropyl-3-pyridyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]pyrrolidin-2-one	

No	Name	Structure
P-4186	[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1S)-1-methylpropyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4187	[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[(3-hydroxy-1-methyl-propyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4188	[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-1-(hydroxymethyl)propyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4189	4-[[5-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]pyrrolidin-2-one	
P-4190	[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-2-hydroxy-1-methyl-ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4191	[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R,3R)-3-hydroxycyclohexyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4192	[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R,2R)-2-hydroxycyclopentyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	

No	Name	Structure
P-4193	1-[3-[[5-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]pyrrolidin-1-yl]ethanone	
P-4194	(2R)-2-[[5-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]cyclohexanone	
P-4195	[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[(1,1-dioxothiolan-3-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4196	[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R,2R)-2-hydroxycyclohexyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4197	[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-2-methoxy-1-methyl-ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4198	4-[[5-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]piperidin-2-one	
P-4199	[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[[(1R)-2,2,2-trifluoro-1-methyl-ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	

No	Name	Structure
P-4200	4-[[5-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-methyl-piperidin-2-one	
P-4201	[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-3-pyridyl]-[4-[(1,1-dioxothian-3-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	
P-4202	1-cyclopropyl-4-[[5-[6-[(4,4-difluorocyclohexyl)amino]-2-fluoro-pyridine-3-carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]pyrrolidin-2-one	

Example 16: Compound properties

[0718] While the inhibitory activity of the compounds on any of Fms, Kit, Flt-3, TrkA, TrkB and TrkC 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 some instances, Fms selectivity relative to Kit and other kinases provides preferred activity for treating certain diseases, such as rheumatoid arthritis, Alzheimer's disease, Parkinson's disease, osteoarthritis, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, or renal hypertrophy. In some instances, Fms selectivity of compounds in combination with the compounds inability to cross the blood brain barrier provides preferred activity for treating certain diseases, such as osteoarthritis, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, or renal hypertrophy. In some instances, Fms selectivity of compounds in combination with the compounds ability to effectively cross the blood brain barrier provides preferred activity for treating certain diseases, such as rheumatoid arthritis, Alzheimer's disease, or Parkinson's disease. In some instances, dual Fms/Kit activity provides preferred activity for treating certain diseases, such as breast cancer, prostate cancer, multiple myeloma, melanoma, acute myeloid leukemia, brain metastases, neurofibromatosis, gastrointestinal stromal tumors, rheumatoid arthritis, or multiple sclerosis. In some instances, dual Fms/Flt-3 activity provides preferred activity for treating certain diseases, such as acute myeloid leukemia. In addition to

demonstrating kinase inhibitory activity against Fms, Kit, Flt-3 or at least both Fms and Kit or at least both Fms and Flt-3 in both biochemical and cell based assays, compounds have improved solubility, improved pharmacokinetic properties, and low Cyp inhibition. The compounds are assessed in the following assays or similar assays available to one skilled in the art.

[0719] Assays for biochemical and cell based activity are known in the art, for example, U.S. Patent Application Publication Number 2009/0076046, the disclosure of which is hereby incorporated by reference as it relates to such assays. For example, in one assay the biochemical activity IC_{50} values are determined with respect to inhibition of c-Kit kinase activity, where inhibition of phosphorylation of a peptide substrate is measured as a function of compound concentration. Compounds to be tested are dissolved in DMSO to a concentration of 20 mM. These are diluted 30 µL into 120 µL of DMSO (4 mM) and 1 µL is added to an assay plate. These are then serially diluted 1:2 (50 µL to 100 µL DMSO) for a total of 8 points. Plates are prepared such that each kinase reaction is 20 µL in 1x kinase buffer (25 mM HEPES, pH 7.5, 2 mM $MgCl_2$, 2 mM $MnCl_2$, 0.01% Tween-20, 1 mM DTT, 0.01% BSA), 5% DMSO and 100 µM ATP. Substrate is 30 nM biotin-(E4Y)10 (Millipore). C-kit kinase (obtained from Millipore (#14-559) or is prepared as described in U.S. Patent Application Publication Number 2009/0076046, the disclosure of which is hereby incorporated by reference as it relates to this assay) is at 0.75 ng per sample. After incubation of the kinase reaction for 1 hour at room temperature, 5 µL of donor beads (Streptavidin coated beads (Perkin Elmer Life Science) final concentration 10 µg/mL) in stop buffer (25 mM Hepes pH 7.5, 100 mM EDTA, 0.01% BSA) is added, the sample is mixed and incubated for 20 minutes at room temperature before adding 5 µL of acceptor beads (PY20 coated beads (Perkin Elmer Life Science) final concentration 10 µg/mL) in stop buffer. The samples are incubated for 60 minutes at room temperature and the signal per well is read on Envision reader. Phosphorylated substrate results in binding of the PY20 antibody 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}.

[0720] In one assay the biochemical activity IC_{50} values are determined with respect to inhibition of Fms kinase activity, where inhibition of phosphorylation of a peptide substrate is measured as a function of compound concentration. Compounds to be tested, dissolved in DMSO (1 µL), are added to a white 384-well plate (Costar #3705). Working stocks of Fms kinase (Invitrogen #PV3249), biotin-$(E4Y)_{10}$ substrate (Upstate Biotech, Cat# 12-440), and ATP (Sigma, Cat#A-3377) are prepared in 25 mM Hepes pH 7.5, 0.5 mM $MgCl_2$, 2 mM $MnCl_2$, 2 mM DTT, 0.01% BSA, and 0.01% Tween-20. All components are added to the 384-well plate for a final concentration of 1 ng/well Fms, 30 nM biotin-$(E4Y)_{10}$ (Upstate Biotechnology) and 100 µM ATP in a volume of 20 µL. Each sample is at 5% DMSO. The plate is then incubated for 20 minutes at 30 °C. Just before use, working stocks of donor and acceptor beads from the AlphaScreen PY20 Detection Kit (PerkinElmer, Cat#676601M)

are prepared in 25 mM Hepes pH 7.5, pH 7.4, 100 mM EDTA, 0.01% BSA. To stop the reaction, the plate is uncovered in the dark and 5 μL of Donor Beads solution (Streptavidin beads) is added to each well. The plate is incubated at room temperature for 20 minutes. Five microliters of Acceptor Beads solution (PY20 coated beads) are then added to each well. The final concentration of each bead is 10 μg/mL. The plates are incubated at room temperature for 60 minutes. Fluorescence signal is recorded on the Envision reader. Phosphorylated substrate results in binding of the PY20 antibody 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}.

[0721] In one assay the biochemical activity IC_{50} values are determined with respect to inhibition of Flt-3 kinase activity, where inhibition of phosphorylation of a peptide substrate is measured as a function of compound concentration. Compounds to be tested, dissolved in DMSO (1 μL), are added to a white 384-well plate (Costar #3705). Working stocks of Flt-3 kinase (Invitrogen), biotin-$(E4Y)_{10}$ substrate (Upstate Biotech, Cat# 12-440), and ATP (Sigma, Cat#A-3377) are prepared in 25 mM Hepes pH 7.5, 5 mM $MgCl_2$, 5 mM $MnCl_2$, 1 mM DTT, and 0.01% Tween-20. All components are added to the 384-well plate for a final concentration of 1 ng/well Flt-3, 30 nM biotin-$(E4Y)_{10}$ and 100 μM ATP in a volume of 20 μL. Each sample is at 5% DMSO. The plate is then incubated for 1 hour at room temperature. Just before use, working stocks of donor and acceptor beads from the AlphaScreen PY20 Detection Kit (PerkinElmer, Cat#676601M) are prepared in 25 mM Hepes pH 7.5, pH 7.4, 100 mM EDTA. 0.3% BSA. To stop the reaction, the plate is uncovered in the dark and 5 μL of Donor Beads solution (Streptavidin beads) is added to each well. The plate is incubated at room temperature for 20 minutes. Five microliters of Acceptor Beads solution (PY20 coated beads) are then added to each well. The final concentration of each bead is 10 μg/mL. The plates are incubated at room temperature for 60 minutes. Fluorescence signal is recorded on the Envision reader. Phosphorylated substrate results in binding of the PY20 antibody 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}.

[0722] In one assay the biochemical activity IC_{50} values are determined with respect to inhibition of TrkA kinase activity, where inhibition of phosphorylation of a peptide substrate is measured as a function of compound concentration. Compounds to be tested, dissolved in DMSO (1 μL), are added to a white 384-well plate (Costar #3705). Working stocks of TrkA kinase (UBI), biotin-$(E4Y)_{10}$ substrate (Upstate Biotech, Cat# 12-440), and ATP (Sigma, Cat#A-3377) are prepared in 25 mM Hepes pH 7.5, 10 mM $MnCl_2$, 1 mM DTT, 0.01 % BSA, and 0.01% Tween-20. All components are added to the 384-well plate for a final concentration of 1 ng/well TrkA, 30 nM biotin-$(E4Y)_{10}$ and 100 μM ATP in a volume of 20 μL. Each sample is at 5% DMSO. The plate is shaken for 1 minute at 1200 rpm, spun for 1 minute at 1000 rpm, then incubated for 40 minutes at room temperature. Just

before use, working stocks of donor and acceptor beads from the AlphaScreen PY20 Detection Kit (PerkinElmer, Cat#676601M) are prepared in 25 mM Hepes pH 7.5, 100 mM EDTA. 0.01% BSA. Donor Beads solution (Streptavidin beads) is added (5 µL) to each well to final bead concentration of 10 µg/mL. The plate is incubated at room temperature for 20 minutes. Acceptor Beads solution (PY20 coated beads) are then added to each well (5 µL) to a final concentration of bead at 10 µg/mL. The plates are incubated at room temperature for 60 minutes. Fluorescence signal is recorded on the Envision reader. Phosphorylated substrate results in binding of the PY20 antibody 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}. Similar assays are used for TrkB and Trk C kinase.

[0723] Compounds are assessed in a variety of cell based assays. For example BaF3 cells engineered with any of BCR-FMS, BCR-KIT, BCR-FLT3, BCR-NTRK1, BCR-NTRK2, and BCR-NTRK3, are used in cell proliferation assays to assess inhibitory acitivity of Fms, Kit, Flt-3, TrkA, TrkB, and TrkC, respectively. An MV-4-11 (leukemia) cell proliferation assay is used to assess inhibitory activity in Flt-3, and SKNSH (human neuroblastoma) cell proliferation assay is used to assess efficacy of Fms/Trk inhibitors. Additional cells may be assayed similarly to assess the efficacy of Fms/Trk inhibitors, such as MiaPaCa (human pancreatic cancer) and Capan-1 (human pancreatic carcinoma) cells. Reagent and assay conditions are as follows:

BaF3 cells:
Maintained in RPMI containing 10% FBS, 1% PenStrep, 1% NEAA, and 1% L-Glutamine, supplemented with 1 mg/mL G418 and 5% WEHI-CM (or recombinant murine IL-3).
Confluent cells are split 1:50 to 1:100 every 3-4 days.

MV-4-11 cells:
Maintained in Iscove's Modified Dulbecco's Medium containing 10% FBS.
Confluent cells are split 1:4 every 3-4 days.

SKNSH cells: RPMI containing 10% FBS.

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:

BaF3: resuspend in growth media + 1 mg/mL G418 (without WEHI/IL-3) to 2 x 10^5 cells/mL.

MV-4-11: resuspend in growth media to 5 x 10^5 cells/mL.

SKNSH: resuspend in growth media to 2 x 10^4 cells/mL.

The cells are plated (50 µL, 150 µL for SKNSH cells) 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:

BaF3: 10,000 cells per well.

MV-4-11: 25,000 cells per well.

SKNSH: 3,000 cells per well.

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 is added to 249 μL growth media and 50 μL is added to a well containing cells, providing 10 μM compound for the maximum concentration point. The cells are incubated for 3 days at 37 °C in 5% CO_2. For SKNSH cells, a 0.75 μL aliquot of appropriate dilution in DMSO is added to 150 μL of cells.

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 to each well as follows:

BaF3: 25 μL per well.

MV-4-11: 40 μL per well.

SKNSH: 20 μL per well.

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.

[0724] Further, an osteoclast differentiation assay is used to assess the efficacy of Fms inhibitors for treating bone disease such as osteoarthritis. On day 0, Osteoclast Medium BulletKit (Lonza catalog # PT-8001, containing Media, FBS, L-Glutamine, PenStrep, RANKL, and M-CSF) media is thawed and the FBS, L-glutamine and PenStrep from the kit is added to 100 mL of Osteoclast Precursor Basal medium to provide the Osteoclast Precursor Growth Medium (OPGM). This is warmed to 37 °C. Osteoclast precursor cells (Lonza catalog # 2T-110) frozen in cryovial are warmed to 37 °C and transferred to a 50 mL conical tube. The cryovial is rinsed with OPGM and added dropwise to the conical tube of cells with swirling, then the volume is adjusted to 20-30 mL with addition of OPGM. The cells are centrifuged at 200 x g for 15 minutes at room temperature and all but approximately 3 mL of supernatant is removed to a new conical tube. The cells are suspended in the remaining supernatant and the volume is adjusted to 10-15 mL with OPGM added dropwise with swirling. The cells are centrifuged at 200 x g for 15 minutes at room temperature and all but approximately 1 mL of supernatant is removed. The cells are resuspended in the remaining supernatant, counted, and the volume adjusted with an appropriate amount of OPGM to provide approximately 1 x 10^5 cells/mL. A 0.1 mL aliquot of cells is added to each well of a 96-well plate. Compound to be tested is prepared in DMSO for plating at a high concentration of 2.5 mM, with 8 point 1:3 serial dilutions. A 1 μL aliquot of each compound dilution is added to a 96 well v-bottom polypropylene plate and 0.124 mL of OPGM is added to the compound. Then 50 μL of the compound in OPGM is added to the osteoclast

precursor cells in 96-well plate (providing highest test concentration of 5 μM). RANKL (2 μg) from the BulletKit is reconstituted in 1 mL of OPGM, then vortexed and centrifuged briefly. A 792 μL aliquot of RANKL is added to 6 mL of OPGM and 50 μL is added to low control wells. Then 76.6 μL M-CSF (10 μg/mL) from the BulletKit is added to the remaining 5.8 mL of OPGM/RANKL solution (4X RANKL/M-CSF/OPGM). A 50 μL aliquot of this is added to the remaining wells, and the remainder is stored at 4 °C for later use. The plate is incubated at 37 °C for 6 days, then the remaining OPGM/RANKL/M-CSF solution is warmed to 37 °C. The remaining approximately 198 μL is combined with 6 mL of OPGM. The media is aspirated from the osteoclast wells and 100 μL of RANKL/OPGM is added to the low controls. The remaining RANKL/OPGM is combined with the approximately 18.5 μL of remaining M-CSF. The remaining 4X RANKL/M-CSF/OPGM from day 0 is diluted to 1X and combined with the freshly prepared solution. A 0.1 mL aliquot of this is added to each osteoclast well and incubated for 37 °C for 1 day. The Acid Phosphatase kit (Cayman Chemical catalog # 10008051) is warmed to room temperature. The assay buffer is diluted 5 mL with 45 mL of water. For each plate, two substrate tablets are dissolved in 4.5 mL of the assay buffer, mixing by vortex to break up the tablet. Stop solution is diluted 12 mL with 36 mL of water. In a tissue culture hood, 20 μL of each osteoclast well supernatant is transferred to a 96 well plate. A 30 μL aliquot of the substrate solution is added to each well and incubated at 37 °C for 20 minutes, then added 100 μL stop solution to each well. The absorbance of each well is read at 405 nM on Safire plate reader. The absorbance reading is plotted vs. concentration to provide the IC_{50} for each compound.

[0725] 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 at or 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.

[0726] The following table indicates the Fms, Kit, Flt3, TrkA, and TrkC biochemical inhibitory activity for the exemplary compounds indicated:

Compound number	Biochemical Inhibition IC_{50} (μM)				
	Fms	Kit	Flt3	TrkA	TrkC
P-3001	< 0.1	< 1	NA	NA	NA

P-3003	< 1	> 1	NA	NA	NA
P-3004	< 0.01	< 1	> 1	NA	NA
P-3005	< 1	> 1	NA	NA	NA
P-3006	< 0.01	< 1	NA	NA	NA
P-3007	< 1	> 1	NA	NA	NA
P-3008	< 0.1	< 1	NA	NA	NA
P-3009	< 0.1	NA	NA	NA	NA
P-3010	< 0.01	< 0.1	< 0.1	< 1	NA
P-3011	< 0.01	< 0.01	< 0.01	> 1	NA
P-3012	< 0.01	< 0.01	< 0.1	> 1	NA
P-3013	< 0.01	< 1	> 1	NA	NA
P-3014	< 0.01	< 0.1	< 1	> 1	NA
P-3015	< 0.01	< 1	< 0.1	> 1	NA
P-3016	< 0.1	< 0.1	< 0.1	> 1	NA
P-3017	< 0.1	< 1	< 0.1	> 1	NA
P-3018	< 0.01	< 0.01	< 0.01	< 1	NA
P-3019	< 0.01	< 1	< 1	< 0.1	< 0.1
P-3020	< 0.01	< 0.01	< 0.01	< 0.1	< 1
P-3021	< 0.01	< 0.01	< 0.01	< 0.1	< 1
P-3022	< 0.1	< 0.1	< 0.1	< 1	< 1
P-3023	< 0.1	< 0.1	NA	NA	NA
P-3024	< 0.1	< 0.01	< 0.01	< 1	> 1
P-3025	< 0.1	< 0.01	< 0.01	< 0.1	< 0.01
P-3026	< 0.01	< 0.01	< 0.1	> 1	< 0.1
P-3027	< 0.01	< 0.01	< 0.01	< 1	< 0.1
P-3028	> 1	< 1	NA	< 0.1	< 0.1
P-3029	< 0.1	< 1	NA	< 1	< 1
P-3030	< 0.1	< 0.1	NA	< 0.01	< 0.01
P-3031	< 1	< 0.1	NA	< 0.1	< 0.1
P-3032	> 1	< 1	NA	> 1	> 1
P-3033	< 0.1	< 0.01	NA	< 0.01	< 0.1
P-3034	< 0.1	< 0.1	NA	< 1	< 1
P-3035	< 1	< 0.1	< 0.1	< 1	< 1
P-3036	< 0.01	< 0.1	< 0.1	< 1	< 1
P-3037	> 1	< 1	NA	NA	NA
P-3038	< 1	< 1	NA	NA	NA
P-3039	< 0.01	< 0.1	< 0.1	< 0.1	NA
P-3040	< 0.1	> 1	< 0.1	< 0.01	NA
P-3041	< 0.01	< 1	< 1	< 1	NA
P-3042	< 0.01	< 0.1	< 1	< 0.1	NA
P-3043	< 0.01	< 1	< 1	< 0.1	NA
P-3044	< 0.01	< 1	< 1	< 0.1	NA
P-3045	< 0.01	< 1	< 0.1	< 0.01	NA
P-3048	< 0.01	< 0.1	NA	< 0.01	NA
P-3049	< 0.01	< 0.1	NA	< 0.01	NA
P-3050	< 0.1	< 0.1	NA	< 0.1	NA
P-3051	< 0.01	< 0.1	NA	< 0.01	NA
P-3052	< 0.1	< 0.1	NA	< 0.01	NA
P-3053	< 0.01	< 0.1	NA	< 0.1	NA
P-4001	< 0.01	< 1	< 1	< 0.1	< 0.01
P-4002	< 0.1	< 1	NA	< 0.1	< 1
P-4003	< 0.1	< 1	< 1	< 1	NA
P-4004	< 0.1	< 0.1	< 0.01	< 0.1	NA

P-4005	< 0.01	< 0.1	< 0.1	< 0.1	NA
P-4006	< 0.01	< 0.1	< 0.1	< 0.1	NA
P-4007	< 0.01	< 0.1	< 0.1	< 0.01	NA
P-4008	< 0.01	< 1	< 0.1	< 0.01	NA
P-4009	< 0.01	< 0.1	< 0.1	< 0.01	NA
P-4010	< 0.01	< 1	< 1	< 1	NA
P-4011	< 0.01	< 1	< 1	< 1	NA
P-4012	< 0.01	< 1	< 1	< 0.1	NA
P-4013	< 0.01	< 1	> 1	< 1	NA
P-4014	< 0.01	< 0.1	< 1	> 1	NA
P-4015	< 0.1	< 0.1	> 1	> 1	NA
P-4016	< 0.01	< 0.1	< 0.01	< 0.01	NA
P-4017	< 0.01	< 0.1	< 0.1	< 0.1	NA
P-4018	< 0.01	< 0.1	< 0.1	< 0.1	NA
P-4019	< 0.01	< 1	< 0.1	< 0.1	NA
P-4020	< 0.01	< 0.1	< 0.1	< 0.01	NA
P-4021	< 0.1	< 1	> 1	< 1	NA
P-4022	< 0.1	< 1	< 0.1	< 0.01	NA
P-4023	< 0.01	< 1	< 1	< 0.1	NA
P-4024	< 1	< 1	< 0.1	< 0.1	NA
P-4025	< 1	> 1	< 1	< 0.1	NA
P-4026	< 0.01	< 1	< 0.1	< 0.01	NA
P-4027	< 0.1	< 0.1	< 0.01	< 0.01	NA
P-4028	< 0.01	< 0.1	< 0.1	< 0.01	NA
P-4029	< 0.01	< 0.1	< 0.01	< 0.01	NA
P-4030	< 0.01	< 1	< 1	< 0.1	NA
P-4031	< 0.1	< 0.1	< 0.1	< 0.1	NA
P-4032	< 0.1	< 0.1	< 0.1	< 0.1	NA
P-4036	< 0.01	< 1	> 1	< 0.1	NA
P-4037	< 0.1	< 1	< 1	< 0.1	NA
P-4038	< 0.1	< 1	NA	< 0.1	NA
P-4039	< 1	< 1	NA	< 0.1	NA
P-4040	< 0.1	< 0.1	NA	< 0.01	NA
P-4041	< 0.1	< 0.1	NA	< 0.01	NA
P-4046	< 0.1	< 1	NA	< 1	NA
P-4047	> 1	> 1	NA	>1	NA
P-4048	< 0.01	< 0.01	NA	< 0.01	NA
P-4049	< 0.01	< 1	NA	< 0.01	NA
P-4050	< 1	< 1	NA	< 1	NA
P-4051	< 1	< 1	NA	< 0.01	NA
P-4052	< 1	> 1	NA	< 1	NA
P-4053	< 0.01	< 1	NA	< 0.01	NA
P-4054	< 0.01	> 1	NA	< 0.1	NA
P-4055	< 0.1	< 1	NA	NA	NA
P-4056	< 0.1	< 0.1	NA	NA	NA
P-4057	< 0.1	> 1	NA	< 1	NA
P-4058	< 0.1	> 1	NA	< 1	NA
P-4059	< 0.1	< 1	NA	< 0.1	NA
P-4060	< 0.01	< 0.1	NA	< 0.01	NA
P-4061	< 0.1	> 1	NA	< 0.1	NA
P-4062	< 0.01	< 0.1	NA	< 0.01	NA
P-4063	< 0.01	< 1	NA	< 0.01	NA
P-4064	< 0.01	< 0.1	NA	< 0.01	NA

P-4065	< 0.01	< 0.1	NA	< 0.01	NA
P-4066	< 0.01	< 0.1	NA	< 0.01	NA
P-4067	< 0.01	< 1	NA	< 0.01	NA
P-4068	< 0.01	< 0.1	NA	< 0.01	NA
P-4069	< 1	> 1	NA	< 0.1	NA
P-4070	> 1	> 1	NA	> 1	NA
P-4071	< 1	> 1	NA	< 0.01	NA
P-4072	< 0.1	> 1	NA	< 0.1	NA
P-4073	< 0.1	< 1	NA	< 0.01	NA
P-4074	< 0.1	< 1	NA	< 0.01	NA
P-4075	< 0.01	< 1	NA	< 0.01	NA
P-4076	< 0.01	< 0.1	NA	< 0.01	NA
P-4077	< 0.1	< 1	NA	< 0.01	NA
P-4078	< 0.01	< 1	NA	< 0.01	NA
P-4079	< 0.01	< 0.1	NA	< 0.01	NA
P-4080	< 0.01	< 1	NA	< 0.01	NA
P-4081	< 0.01	< 0.1	NA	< 0.01	NA
P-4082	< 0.1	< 1	NA	< 0.01	NA
P-4083	< 0.01	< 0.1	NA	< 0.01	NA
P-4084	< 0.01	< 0.1	NA	< 0.01	NA
P-4085	< 0.01	< 1	NA	< 0.01	NA
P-4086	< 1	< 1	NA	< 0.1	NA
P-4087	< 0.1	< 0.1	NA	< 0.01	NA
P-4088	< 0.1	< 1	NA	< 0.01	NA
P-4089	< 0.1	< 1	NA	< 0.1	NA
P-4090	< 0.1	< 1	NA	< 0.1	NA
P-4091	< 0.1	< 0.1	NA	< 0.01	NA
P-4092	< 0.01	< 0.1	NA	< 0.01	NA
P-4093	< 0.01	< 0.1	NA	< 0.01	NA
P-4094	< 0.01	< 0.01	NA	< 0.01	NA
P-4095	< 0.01	< 0.1	NA	< 0.01	NA
P-4096	< 0.1	< 1	NA	< 0.1	NA
P-4097	< 1	< 1	NA	< 0.1	NA
P-4098	< 0.01	< 0.1	NA	< 0.01	NA
P-4099	< 0.1	< 0.1	NA	< 0.1	NA
P-4100	< 0.1	< 0.1	NA	< 0.1	NA
P-4101	< 0.1	< 1	NA	< 0.1	NA
P-4102	< 0.1	< 1	NA	< 0.1	NA
P-4103	< 1	< 1	NA	< 0.1	NA
P-4104	< 1	< 1	NA	< 0.1	NA
P-4105	< 0.1	> 1	NA	< 0.1	NA
P-4106	< 0.1	< 1	NA	< 0.01	NA
P-4107	< 0.1	< 0.1	NA	< 0.01	NA
P-4108	< 0.1	< 1	NA	< 0.1	NA
P-4109	< 0.1	< 1	NA	< 0.1	NA
P-4110	< 0.1	< 1	NA	< 1	NA
P-4111	< 0.1	< 1	NA	< 0.1	NA
P-4112	< 0.1	< 1	NA	< 0.1	NA
P-4113	< 0.01	< 0.1	NA	< 0.01	NA
P-4114	< 0.01	< 0.1	NA	< 0.01	NA
P-4115	< 0.01	< 0.1	NA	< 0.01	NA
P-4116	< 0.1	< 0.1	NA	< 0.01	NA
P-4117	< 0.01	< 0.1	NA	< 0.01	NA

P-4118	< 0.1	< 0.1	NA	< 0.01	NA
P-4119	< 0.01	< 0.01	NA	< 0.01	NA
P-4120	< 0.1	< 0.1	NA	< 0.1	NA
P-4121	< 0.1	< 0.01	NA	< 0.1	NA
P-4122	< 0.01	< 0.01	NA	< 0.01	NA
P-4123	< 0.01	< 0.01	NA	< 0.01	NA
P-4124	< 0.01	< 0.01	NA	< 0.01	NA
P-4125	< 0.1	< 0.1	NA	< 0.01	NA
P-4126	< 0.01	< 0.1	NA	< 0.01	NA
P-4127	< 0.1	< 1	NA	< 0.1	NA
P-4128	< 0.1	> 1	NA	< 1	NA
P-4129	< 0.1	< 1	NA	< 1	NA
P-4130	< 0.01	< 1	NA	< 0.01	NA

[0727] The following table indicates the inhibition of cell proliferation for BCR-FMS, BCR-KIT, BCR-FLT3, BCR-NTRK1, BCR-NTRK2 and BCR-NTRK3 BaF3 cells, MV-4-11 cells and SKNSH cells for the exemplary compounds indicated:

Comp. number	Inhibition of Cell Proliferation IC_{50} (μM)						
	BCR/BaF3					MV-4-11	SKNSH
	Fms	Kit	TrkA	TrkB	TrkC		
P-3001	< 0.1	> 1	-	-	-	NA	NA
P-3003	< 1	> 1	NA	NA	NA	NA	NA
P-3004	< 0.1	> 1	< 10	< 10	< 10	< 10	NA
P-3005	< 1	> 1	-	-	-	NA	NA
P-3006	< 1	> 1	< 20	-	-	NA	NA
P-3007	< 1	-	-	-	-	NA	NA
P-3008	< 0.1	> 1	NA	NA	NA	NA	NA
P-3009	< 1	> 1	-	-	-	NA	NA
P-3010	< 0.1	< 1	-	-	-	NA	NA
P-3011	< 0.1	< 0.1	< 1	< 1	< 0.1	NA	NA
P-3012	< 0.1	< 1	< 1	< 1	< 1	NA	NA
P-3013	< 0.1	> 1	-	-	-	< 10	NA
P-3014	< 0.1	> 1	-	-	-	NA	NA
P-3015	< 1	> 1	-	-	-	NA	NA
P-3016	< 1	> 1	-	-	-	NA	NA
P-3017	< 1	> 1	-	-	-	NA	NA
P-3018	< 0.1	< 0.1	< 1	< 0.1	< 0.1	< 0.01	NA
P-3019	< 0.01	< 1	< 0.1	< 0.1	< 0.1	< 1	< 10
P-3020	< 0.01	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 1
P-3021	< 0.01	< 0.1	< 1	< 0.1	< 0.1	NA	< 1
P-3022	< 0.1	< 0.1	< 1	< 1	< 1	< 1	NA
P-3023	< 0.1	< 0.1	< 1	< 1	< 1	< 0.1	NA
P-3024	< 0.01	< 0.1	< 1	< 1	< 0.1	NA	< 1
P-3025	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	NA	< 1
P-3026	< 0.01	< 0.1	< 0.1	< 0.1	< 0.1	NA	-
P-3027	< 0.01	< 0.1	< 0.1	< 1	< 0.1	< 0.01	-
P-3028	< 1	< 0.1	< 0.1	< 1	< 0.1	NA	< 20
P-3029	< 0.1	< 1	> 1	> 1	< 1	NA	-
P-3030	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	NA	< 0.1
P-3031	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	NA	< 0.1

P-3032	< 1	< 1	< 1	> 1	< 1	NA	< 1
P-3033	< 0.01	< 0.01	< 0.1	< 0.1	< 0.1	NA	< 1
P-3034	< 0.01	< 0.1	< 0.1	< 1	< 0.1	NA	< 1
P-3035	< 0.1	< 1	< 1	< 1	< 0.1	< 1	< 1
P-3036	< 0.01	< 0.1	< 1	< 1	< 1	< 0.1	< 20
P-3037	> 1	> 1	> 1	-	> 1	NA	-
P-3038	< 1	< 1	< 1	> 1	< 1	> 1	-
P-3039	< 0.01	< 1	< 1	< 1	< 0.1	< 1	> 1
P-3040	< 0.1	> 1	< 0.1	< 0.01	< 0.01	NA	> 1
P-3041	< 0.01	< 1	< 1	< 1	< 0.1	NA	> 1
P-3042	< 0.1	< 1	< 1	< 0.1	< 0.1	NA	> 1
P-3043	< 0.1	< 1	< 0.1	< 0.1	< 0.1	NA	< 1
P-3044	< 0.1	< 1	< 1	< 0.1	< 0.1	NA	> 1
P-3045	< 0.1	< 1	< 0.1	< 0.01	< 0.1	NA	-
P-3048	< 0.01	< 0.1	< 0.1	NA	NA	NA	NA
P-3049	< 0.01	< 0.1	< 0.01	NA	NA	NA	NA
P-3050	< 0.1	< 1	< 0.1	NA	NA	NA	NA
P-3051	< 0.1	< 1	< 0.1	NA	NA	NA	NA
P-3052	< 0.1	NA	< 0.1	NA	< 0.01	NA	NA
P-3053	< 0.01	NA	< 0.1	NA	< 0.01	NA	NA
P-4001	< 0.01	< 1	< 0.1	< 0.1	< 0.01	< 1	< 1
P-4002	< 0.1	< 1	< 1	< 1	< 0.1	NA	< 0.1
P-4003	< 0.1	> 1	< 1	< 1	< 0.1	< 1	> 1
P-4004	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	< 1	< 1
P-4005	< 0.01	< 0.1	< 0.1	< 0.01	< 0.01	< 1	< 1
P-4006	< 0.01	< 0.1	< 0.1	< 0.01	< 0.01	< 0.1	< 0.1
P-4007	< 0.01	< 1	< 0.01	< 0.1	< 0.01	< 1	< 1
P-4008	< 0.01	< 1	< 0.1	< 0.1	< 0.1	< 0.1	> 1
P-4009	< 0.01	< 1	< 0.1	< 0.01	< 0.01	< 0.1	< 0.1
P-4010	< 0.01	< 1	< 1	< 0.1	< 0.1	< 1	< 1
P-4011	< 0.01	> 1	< 1	< 1	< 1	< 1	> 1
P-4012	< 0.01	< 1	< 1	< 0.1	< 0.1	< 1	> 1
P-4013	< 0.01	< 1	< 1	< 1	< 1	< 1	> 1
P-4014	< 0.1	> 1	< 1	< 1	< 1	< 1	> 10
P-4015	< 0.01	> 1	< 1	< 1	< 0.1	< 1	> 1
P-4016	< 0.01	< 0.1	< 0.1	< 0.01	< 0.01	< 0.1	> 1
P-4017	< 0.01	< 1	< 1	< 1	< 0.1	< 1	< 1
P-4018	< 0.01	< 1	< 0.1	< 0.1	< 0.01	< 1	< 1
P-4019	< 0.01	< 1	< 1	< 0.1	< 0.1	< 1	> 1
P-4020	< 0.1	< 1	< 1	< 0.1	< 0.1	NA	< 1
P-4021	< 1	> 1	> 1	< 1	< 1	NA	< 1
P-4022	< 0.1	< 1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4023	< 0.01	< 1	< 0.1	< 0.1	< 0.01	NA	< 1
P-4024	< 0.1	< 1	< 0.1	< 0.1	< 0.1	NA	> 1
P-4025	< 0.1	> 1	< 0.1	< 0.1	< 0.1	NA	> 1
P-4026	< 0.01	< 1	< 0.1	< 0.01	< 0.01	NA	NA
P-4027	< 0.1	< 1	< 0.1	< 0.01	< 0.01	NA	NA
P-4028	< 0.01	< 1	< 0.01	< 0.01	< 0.01	NA	NA
P-4029	< 0.1	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4030	< 0.01	< 1	< 1	< 0.1	< 0.1	NA	NA
P-4031	< 0.1	< 1	< 0.1	< 0.01	< 0.01	NA	NA
P-4032	< 0.1	< 1	< 0.1	< 0.1	< 0.1	NA	NA
P-4036	< 0.1	< 1	< 1	< 0.1	< 0.1	NA	NA

P-4037	< 0.1	< 0.1	< 0.1	NA	NA	NA	NA
P-4038	< 0.1	< 1	< 1	< 1	< 0.1	NA	NA
P-4039	< 0.1	< 1	< 0.1	< 0.1	< 0.1	NA	NA
P-4040	< 0.1	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4041	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4046	< 0.1	< 1	< 1	< 1	< 1	NA	< 10
P-4047	>1	> 1	> 1	> 1	> 1	NA	NA
P-4048	< 0.01	< 1	< 1	< 0.01	< 0.01	NA	< 1
P-4049	< 1	< 1	< 1	< 1	< 1	NA	< 1
P-4050	< 1	> 1	< 1	< 1	< 1	NA	< 1
P-4051	< 1	> 1	< 1	< 0.01	< 0.01	NA	< 1
P-4052	< 1	> 1	< 1	< 1	< 0.01	NA	> 1
P-4053	< 1	< 1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4054	< 1	< 1	< 1	< 1	< 0.01	NA	< 10
P-4055	< 1	> 1	< 1	< 0.01	< 0.01	NA	< 1
P-4056	< 1	> 1	< 1	< 0.01	< 0.01	NA	< 1
P-4057	< 1	> 1	> 1	> 1	< 1	NA	< 10
P-4058	< 0.1	< 1	< 1	< 1	< 0.1	NA	< 10
P-4059	< 0.1	> 1	< 1	< 0.1	< 0.1	NA	< 1
P-4060	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 0.1
P-4061	< 0.1	> 1	< 0.1	< 0.01	< 0.01	NA	NA
P-4062	< 0.1	< 1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4063	< 0.1	< 0.1	< 0.01	< 0.1	< 0.01	NA	< 1
P-4064	< 0.1	< 0.1	< 0.1	< 0.01	< 0.01	NA	NA
P-4065	< 0.1	< 0.1	< 0.1	< 0.01	< 0.01	NA	< 1
P-4066	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	NA	NA
P-4067	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4068	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4069	>1	> 1	> 1	> 1	> 1	NA	NA
P-4070	>1	> 1	> 1	> 1	> 1	NA	NA
P-4071	< 0.1	< 0.1	< 0.1	< 0.1	< 0.01	NA	NA
P-4072	< 0.1	< 1	< 0.01	< 0.01	< 0.01	NA	NA
P-4073	< 0.1	< 1	< 0.1	< 0.01	< 0.01	NA	NA
P-4074	< 1	< 1	< 0.1	< 0.1	< 0.01	NA	NA
P-4075	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4076	< 0.1	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4077	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4078	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4079	< 0.1	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4080	< 0.1	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4081	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4082	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4083	< 0.1	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4084	< 0.01	< 1	< 0.1	< 0.01	< 0.01	NA	< 10
P-4085	< 1	> 1	< 1	NA	< 0.1	NA	NA
P-4086	NA	NA	< 0.01	NA	NA	NA	NA
P-4087	< 1	> 1	< 1	< 0.1	< 0.01	NA	NA
P-4088	< 0.1	< 1	< 0.1	< 0.1	< 0.01	NA	NA
P-4089	< 0.1	< 1	< 1	< 0.1	< 0.01	NA	< 10
P-4090	< 0.1	< 1	< 0.1	< 0.01	< 0.01	NA	< 1
P-4091	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 0.1
P-4092	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4093	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA

P-4094	< 0.1	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4095	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4096	< 0.01	< 1	< 0.01	< 0.01	NA	NA	< 10
P-4097	< 0.1	< 1	< 0.1	< 0.1	NA	NA	< 10
P-4098	< 0.1	< 0.1	< 0.01	< 0.01	NA	NA	< 10
P-4099	< 0.01	< 0.1	< 0.01	< 0.01	NA	NA	< 1
P-4100	< 0.1	< 1	< 0.01	< 0.01	NA	NA	< 1
P-4101	< 0.01	< 1	< 0.1	< 0.01	NA	NA	< 1
P-4102	< 0.01	< 1	< 1	< 0.1	NA	NA	< 1
P-4103	< 0.1	> 1	< 1	> 1	> 1	NA	> 1
P-4104	< 0.1	> 1	< 0.1	< 0.1	< 0.1	NA	< 1
P-4105	< 0.1	> 1	< 0.1	< 1	< 1	NA	< 10
P-4106	< 0.1	< 1	< 0.1	< 0.1	< 0.01	NA	< 1
P-4107	< 0.1	< 1	< 0.1	< 0.1	< 0.01	NA	< 1
P-4108	< 0.1	> 1	< 1	< 1	< 0.1	NA	> 1
P-4109	< 0.1	< 1	< 1	< 1	NA	NA	< 10
P-4110	< 0.1	< 1	>1	> 1	NA	NA	< 10
P-4111	< 0.1	< 1	< 0.01	< 0.01	< 0.01	NA	NA
P-4112	< 0.1	> 1	< 0.1	< 0.1	< 0.01	NA	< 10
P-4113	< 0.01	< 1	< 0.1	NA	NA	NA	NA
P-4114	< 0.01	< 1	< 0.01	NA	NA	NA	NA
P-4115	< 0.01	< 1	< 0.1	< 0.1	< 0.01	NA	NA
P-4116	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4117	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4118	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4119	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4120	< 0.1	< 1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4121	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4122	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4123	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 0.1
P-4124	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4125	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4126	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 0.1
P-4127	< 0.01	< 0.1	< 1	< 0.1	< 0.1	NA	< 10
P-4128	< 0.1	< 1	< 1	< 0.1	< 0.1	NA	> 1
P-4129	< 0.1	< 1	< 1	< 0.1	< 0.1	NA	> 10
P-4130	< 0.01	> 1	< 0.1	< 0.01	< 0.01	NA	< 10

[0728] Compounds P-3001, P-3004, P-3006, P-3008, P-3013, P-3019, P-3027, P-3036, P-3039, P-3040, P-3041, P-3042, P-3043, P-3044, P-3045, P-4001, P-4004, P-4005, P-4006, P-4007, P-4008, P-4009, P-4010, P-4011, P-4012, P-4013, P-4014, P-4015, P-4016, P-4017, P-4022, P-4023, P-4024, ,P-4025, and P-4026 to P-4130 were assessed and showed activity in the osteoclast differentiation assay, where compounds P-3004, P-3006, P-3008, P-3019, P-3027, P-3036, P-3039, P-3041, P-3042, P-4001, P-4004, P-4005, P-4006, P-4007, P-4008, P-4009, P-4010, P-4011, P-4012, P-4013, P-4014, P-4015, P-4016, and P-4023 demonstrated an IC_{50} below 0.1 μM in this assay.

[0729] Compounds also demonstrate in vivo activity in a splenomegaly mouse model, where BaF3 cell growth in the spleens of nude mice may show inhibition with compound treatment. BaF3 cells

are engineered with any of BCR-FMS, BCR-TRK1 or BCR-TRK2 to assess in vivo inhibitory effects of Fms, TrkA or TrkB inhibition, respectively. BaF3 cells are maintained in growth media (RPMI containing 10% FBS, 1% PenStrep, 1% NEAA, and 1% L-Glutamine, supplemented with 5% murine IL-3 and 1 mg/mL G418). Four days prior to start, 2 x 10^6 cells are inoculated into a T150 vented flask using the growth media and incubated at 37 °C in 5% CO_2 for three days. One day prior to start, cells are collected by centrifugation and re suspended in growth media without IL-3. On the day of cell implant, the cells are collected by centrifugation, rinsed 3x 20 mL with RPMI, then re suspended in 5.4 mL of media and counted, then adjusted with additional RPMI as needed to give 5 x 10^7 cells/mL. On day 1, female nu/nu mice at 5-6 weeks of age are injected intravenously with BaF3 cells injected injecting 0.1 mL (5 x 10^6) cells in the tail vein (mice without cell injected are included as control group). Compound stocks in dimethylsulfoxide are stored at room temperature protected from light. Stocks are diluted prior to dosing, diluting 22 µL of compound stock into 858 µL of diluent (or 50 µL into 1950 µL) to provide vehicle of 1.0% Polysorbate 80, 0.5% hydroxypropyl methyl cellulose, with final dimethylsulfoxide at 2.5% in all dosing suspensions and vehicle control. Dosing suspension is prepared prior to use, mixing by inversion and sonication in a water bath to make a uniform suspension. On days 10-18, mice are treated with vehicle only or the desired level of compound in vehicle, ~0.2 mL per 25 gm mouse, once a day by oral gavage, or in some instances, twice per day. On day 18, mice are administered a final dose and two hours later a plasma sample is taken. At four hours following the final dose, mice are sacrificed, an additional plasma sample is collected and mouse spleens are removed and weighed. The average spleen weight of vehicle control group mice is compared to the average spleen weight of the test compound mice. Percent spleen growth inhibition is calculated as 100 x [(spleen weight vehicle control-spleen weight test compound) / spleen weight vehicle control]. In some instances, the compounds were not tested in all of the assays as indicated by NA in the table below.

[0730] The following table provides data indicating the percent spleen growth inhibition for exemplary compounds indicated (dosed once per day at 10 mg per kg unless indicated otherwise) in the splenomegaly mouse model:

Comp. number	% spleen growth inhibition		
	Fms	TrkA	TrkB
P-3004	43	NA	NA
P-3010	47	NA	NA
P-3013	48	NA	NA
P-3019	40	NA	14
P-3027	42	NA	2
P-3045	11	NA	NA
P-4004	36	16	41
P-4004*	70	40	91
P-4005	65	25	35
P-4006	55	NA	21
P-4007	28	NA	19

P-4012	24	NA	NA
P-4022	42	NA	33
P-4026	41	NA	NA
P-4027	-1.4	NA	NA
P-4028	86	NA	88
P-4029	66	NA	NA
P-4030	58	NA	50
P-4031	29	NA	NA
P-4053	69	NA	NA
P-4090[#]	38	NA	NA
P-4084	6.2	NA	NA
P-4062	76	NA	NA
P-4061	48	NA	NA
P-4112	9.5	NA	NA
P-4110	30	NA	NA
P-4124	20	NA	NA
P-4120	37	NA	NA
P-4123[#]	14	NA	NA
P-4130	70	NA	NA
P-4128	15	NA	NA

* Dosed at 30 mg/kg.

[#] Dosed at 5 mg/kg.

[0731] 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.

[0732] 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.

[0733] 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-3001	H	L	L	L
P-3004	H	L	L	L
P-3010	H	L	L	M
P-3011	L	L	L	L
P-3012	M	M	M	M
P-3013	L	L	L	L
P-3014	H	M	M	M
P-3018	H	M	M	M
P-3019	H	L	L	L
P-3039	H	M	M	M
P-3040	M	M	M	M
P-3043	M	M	M	M
P-3044	L	L	L	M
P-3045	M	M	M	L
P-4001	M	M	M	M
P-4002	H	M	M	M
P-4003	M	M	M	M
P-4004	M	M	L	L
P-4005	M	L	L	L
P-4006	H	L	L	L
P-4007	M	L	L	L
P-4008	M	M	M	M
P-4009	H	M	L	L
P-4010	H	M	L	L
P-4011	M	M	M	M
P-4012	M	L	L	L
P-4013	H	M	M	M
P-4014	M	M	M	M
P-4015	M	M	M	M
P-4016	M	H	M	M
P-4017	M	M	M	L
P-4018	M	L	L	L
P-4019	M	L	L	L
P-4022	H	M	L	L
P-4023	H	M	L	L
P-4024	M	L	M	M
P-4025	M	L	L	L
P-4036	H	M	L	L

P-4037	H	M	M	M
P-4048	H	M	M	M
P-4049	H	L	L	L
P-4050	H	L	L	L
P-4051	H	M	M	L
P-4052	L	L	L	L
P-4053	H	M	M	M
P-4054	H	M	M	M
P-4055	M	M	L	L
P-4056	M	M	M	L
P-4057	L	L	L	M
P-4058	M	L	L	L
P-4059	M	L	L	L
P-4060	H	M	M	M
P-4061	M	L	M	M
P-4062	H	L	M	L
P-4063	M	M	M	M
P-4064	H	M	L	L
P-4065	H	M	M	M
P-4066	M	L	L	M
P-4067	H	M	M	M
P-4068	H	M	M	M
P-4069	M	L	M	M
P-4070	H	M	M	M
P-4071	M	M	M	M
P-4072	M	L	L	L
P-4073	M	L	L	L
P-4074	H	M	M	M
P-4075	M	L	L	L
P-4076	M	M	M	L
P-4077	M	L	L	L
P-4078	M	L	L	L
P-4079	H	M	M	M
P-4080	M	M	H	M
P-4081	H	M	H	M
P-4082	M	L	L	L
P-4083	M	M	M	H
P-4084	M	M	M	H
P-4087	H	M	M	M
P-4088	H	M	M	M
P-4089	H	M	M	M
P-4090	M	M	M	M
P-4091	H	M	M	M
P-4092	M	M	M	M
P-4093	H	L	L	L
P-4094	H	L	M	M
P-4095	M	M	M	M
P-4096	H	L	L	L
P-4097	M	L	L	L
P-4098	H	L	M	M
P-4099	H	L	L	L
P-4100	H	M	M	M
P-4101	M	L	L	L

P-4102	H	M	M	M
P-4103	L	M	M	M
P-4104	M	L	L	L
P-4105	M	M	M	M
P-4106	M	M	L	M
P-4107	M	M	M	M
P-4108	H	M	M	M
P-4109	L	L	L	L
P-4110	M	L	L	L
P-4111	H	L	L	L
P-4112	M	M	M	H
P-4114	H	L	L	L
P-4115	H	M	M	M
P-4116	H	M	M	M
P-4117	H	L	L	L
P-4118	H	M	M	L
P-4119	H	M	M	L
P-4120	L	M	M	M
P-4121	H	H	H	H
P-4122	H	L	M	L
P-4123	H	L	L	L
P-4124	M	L	L	M
P-4125	H	L	L	L
P-4127	H	M	M	M
P-4128	H	M	M	M
P-4129	H	M	M	M
P-4130	H	M	M	M

[0734] 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.

[0735] Compounds are dissolved in DMSO 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% DMSO). 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.

[0736] 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-3001	> 10	> 10	> 10	> 10	> 10	> 10
P-3004	> 10	5-10	> 10	> 10	> 10	> 10
P-3006	> 10	> 10	> 10	> 10	> 10	NA
P-3008	> 10	< 5	5-10	> 10	5-10	NA
P-3009	> 10	< 5	> 10	> 10	5-10	NA
P-3010	> 10	> 10	> 10	> 10	> 10	> 10
P-3011	> 10	> 10	> 10	> 10	> 10	> 10
P-3012	> 10	> 10	> 10	> 10	> 10	> 10
P-3013	5-10	< 5	> 10	> 10	> 10	> 10
P-3018	> 10	> 10	> 10	> 10	< 5	> 10
P-3019	> 10	< 5	> 10	> 10	> 10	> 10
P-3039	> 10	> 10	> 10	> 10	> 10	NA
P-3040	> 10	> 10	> 10	> 10	> 10	> 10
P-3041	> 10	> 10	> 10	> 10	5-10	> 10
P-3043	> 10	> 10	> 10	> 10	> 10	> 10
P-3044	> 10	> 10	> 10	> 10	> 10	> 10
P-3048	> 10	< 5	> 10	> 10	> 10	> 10
P-3049	> 10	> 10	> 10	> 10	> 10	> 10
P-3050	> 10	> 10	> 10	> 10	> 10	> 10
P-3051	> 10	> 10	> 10	> 10	> 10	> 10
P-3052	> 10	5-10	5-10	> 10	> 10	> 10
P-3053	> 10	> 10	> 10	> 10	> 10	> 10
P-4001	> 10	< 5	> 10	> 10	> 10	NA
P-4002	> 10	> 10	> 10	> 10	> 10	> 10
P-4003	> 10	> 10	> 10	> 10	> 10	> 10
P-4004	> 10	> 10	> 10	> 10	> 10	> 10
P-4005	> 10	> 10	> 10	> 10	> 10	> 10
P-4006	> 10	> 10	> 10	> 10	> 10	> 10
P-4007	> 10	> 10	> 10	> 10	> 10	> 10
P-4008	> 10	> 10	> 10	> 10	5-10	> 10
P-4009	> 10	5-10	> 10	> 10	> 10	> 10
P-4010	> 10	> 10	> 10	> 10	> 10	> 10
P-4011	> 10	> 10	5-10	> 10	5-10	> 10
P-4012	> 10	> 10	> 10	> 10	> 10	> 10
P-4013	> 10	> 10	< 5	> 10	> 10	> 10
P-4014	> 10	> 10	5-10	< 5	5-10	> 10
P-4015	> 10	> 10	> 10	> 10	> 10	> 10
P-4016	> 10	> 10	> 10	> 10	> 10	> 10
P-4017	> 10	> 10	> 10	> 10	> 10	> 10
P-4018	> 10	< 5	> 10	> 10	5-10	> 10
P-4019	> 10	5-10	> 10	> 10	5-10	> 10
P-4022	> 10	5-10	> 10	5-10	5-10	> 10

P-4023	> 10	< 5	> 10	5-10	< 5	> 10
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P-4025	> 10	5-10	> 10	> 10	< 5	> 10
P-4028	> 10	5-10	5-10	> 10	> 10	> 10
P-4029	> 10	> 10	> 10	> 10	> 10	> 10
P-4030	> 10	5-10	> 10	> 10	> 10	> 10
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P-4036	5-10	5-10	5-10	> 10	5-10	5-10
P-4037	> 10	> 10	5-10	> 10	5-10	5-10
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P-4070	> 10	> 10	> 10	> 10	> 10	> 10
P-4071	> 10	> 10	> 10	> 10	> 10	> 10
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P-4112	< 5	< 5	< 5	< 5	> 10	> 10
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P-4117	5-10	> 10	5-10	> 10	> 10	> 10
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P-4121	> 10	5-10	> 10	> 10	> 10	> 10
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P-4123	> 10	> 10	> 10	> 10	> 10	> 10
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P-4127	> 10	5-10	> 10	> 10	< 5	< 5
P-4128	> 10	> 10	> 10	> 10	> 10	> 10
P-4129	> 10	> 10	5-10	5-10	< 5	< 5
P-4130	> 10	< 5	> 10	> 10	< 5	> 10

[0737] 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.

[0738] Analysis of penetration of compound into the brain can be assessed similarly. Each compound is prepared as a 100 mg/mL stock solution in dimethyl sulfoxide, as well as control compounds atenolol at 100 mg/mL and antipyrine at 50 mg/mL. In a cassette format, up to three test compounds, along with atenolol and antipyrine, are combined, 180 μL each, and added to 17.1 mL of 1% methylcellulose. The compounds are in a suspension that is administered in a single dose (10 mL per kg body weight) to 2 groups of CD rats (8-9 weeks, n=3 per group) by oral gavage, an additional group of rats dosed with vehicle only. One group of compound treated rats is sacrificed at 2 hours post dosing, the other group at 6 hours. Plasma is collected in Li-heparin and the brains are collected, cut into right and left hemispheres, weighed and flash frozen. Brain homogenate (30%) and plasma samples are assessed by equilibrium dialysis using a 96 well equilibrium dialysis apparatus with a 5K MW cut off membrane (The Nest Group, Inc.) as per the vendor's protocol with the samples on one side of the dialysis membrane and an equal volume of 1XPBS on the other side. The apparatus is incubated overnight at 37 °C on a plate rotator (The Nest Group, Inc.). The compound concentrations on both sides are analyzed by LC/MS/MS to calculate the mass balance recovery. The concentration in the PBS side is calculated using a standard curve generated for each compound. The PBS concentration is the free compound concentration, while the side with the biological sample provides the concentration in plasma or brain.

Example 17: Efficacy of Compounds in Combination with Standard-of-Care Chemotherapeutic agents in four human cancer cell lines.

[0739] 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 are hereby incorporated by reference with respect to such assays.

[0740] 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.

[0741] 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.

[0742] 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.

[0743] 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.

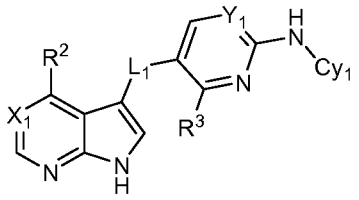
[0744] Also, unless indicated to the contrary, where various numerical values are provided for embodiments, additional embodiments are described by taking any 2 different values as the endpoints of a range. Such ranges are also within the scope of the described invention.

[0745] 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 salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof,

wherein:

X_1 is –N=, -C(H)=, or -C(R^1)= ;

Y_1 is –N= and R^3 is hydrogen; or Y_1 is -C(H)= and R^3 is fluoro or chloro;

L_1 is -C(H_2)- or -C(O)-;

Cy_1 is cycloalkyl optionally substituted with one or more R^4, phenyl optionally substituted with one or more R^5, or 5 or 6 membered heteroaryl optionally substituted on an available carbon atom with one or more R^6 and optionally substituted on an available nitrogen atom with R^7;

when X_1 is -C(R^1)=, R^2 is hydrogen;

when X_1 is –N= or -C(H)=, R^2 is selected from the group consisting of hydrogen, cycloalkyl, lower alkyl optionally substituted with one or more R^8, -N(R^{9a})(R^{9b}), and -O-R^9;

R^1 is fluoro, chloro, or lower alkyl optionally substitituted with one or more fluoro;

each R^4 is independently selected from the group consisting of fluoro, -OH, lower alkyl optionally substitituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro;

each R^5 is independently selected from the group consisting of fluoro, chloro, -O-R^{10}, -S-R^{11}, -S(O_2)-R^{12}, and lower alkyl optionally substitituted with one or more R^{13};

each R^6 is independently selected from the group consisting of fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with one or more fluoro, and lower alkoxy optionally substituted with one or more fluoro; or two R^6 bound to adjacent carbon atoms of the heteroaryl ring form a fused cycloalkyl ring;

R^7 is cycloalkyl, lower alkoxy or lower alkyl optionally substituted with one or more fluoro;

R^8 is fluoro or lower alkoxy optionally substitituted with one or more fluoro;

R^{9a} is H and R^{9b} is selected from the group consisting of (i) H, lower alkyl, lower alkyl substituted with one or more fluoro, lower alkyl substituted with lower alkoxy or lower alkyl substituted with hydroxyl and (ii) cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, each of which is optionally substituted with one to three members selected from lower alkyl, haloalkyl, lower alkoxy or fluoro; or

R^{9a} and R^{9b} together with the nitrogen to which they are attached form a 5- or 6-membered ring having from 0 to 1 additional heteroatom selected from O, N or S, each of which is optionally substituted with one to three members selected from lower alkyl, haloalkyl, lower alkoxy or fluoro;

R^9 is lower alkyl, lower alkyl substituted with one or more fluoro, or lower alkyl substituted with lower alkoxy;

each R^{10}, R^{11} and R^{12} are independently lower alkyl optionally substituted with one or more fluoro; and

each R^{13} is independently selected from the group consisting of fluoro, -OH, and lower alkoxy optionally substituted with one or more fluoro.

2. The compound of claim **1**, wherein X_1 is N, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

3. The compound of claim **2**, wherein L_1 is CH_2, Y_1 is CH and R^3 is F, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

4. The compound of claim **2**, wherein L_1 is CH_2, Y_1 is N and R^3 is F, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

5. The compound of claim **2**, wherein L_1 is -C(=O)-, Y_1 is CH and R^3 is F, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

6. The compound of claim **2**, wherein L_1 is -C(=O)-, Y_1 is N and R^3 is F, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

7. The compound of claim **1**, wherein X_1 is $-C(R^1)=$, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

8. The compound of claim **7**, wherein L_1 is CH_2, Y_1 is CH and R^3 is F, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

9. The compound of claim **7**, wherein L_1 is -C(=O)-, Y_1 is CH and R^3 is F, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

10. The compound of claim **7**, wherein L_1 is $-CH_2-$, Y_1 is N and R^3 is F, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

11. The compound of claim **7**, wherein L_1 is -C(=O)-, Y_1 is N and R^3 is F, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

12. The compound of claim **1**, wherein X_1 is N and R^2 is $-N(R^{9a})(R^{9b})$, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

13. The compound of any of claims **1-12**, wherein Cy_1 is cycloalkyl optionally substituted with one or more R^4, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

14. The compound of claim **13**, wherein Cy_1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl, each of which is optionally substituted with from 1 to 3 R^4, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

15. The compound of any of claims **1-12**, wherein Cy_1 is phenyl optionally substituted with one or more R^5, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

16. The compound of any of claims **1-12**, wherein Cy_1 is 5 or 6-membered heteroaryl optionally substituted on an available carbon atom with one or more R^6 and optionally substituted on an available nitrogen atom with R^7, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

17. The compound of claim **16**, wherein Cy_1 is 3-pyridyl, 2-pyrrolyl, 3-pyrrolyl or 4-pyrazolyl, optionally substituted on an available carbon atom with from 1 to 3 R^6 and optionally substituted on an available nitrogen atom with R^7, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

18. The compound of claim **16** or **17**, wherein each R^6 is independently selected from the group consisting of fluoro, chloro, bromo, cycloalkyl, lower alkyl optionally substituted with from one to three fluoro, and lower alkoxy optionally substituted with one to three fluoro; or two R^6 bound to adjacent carbon atoms of the heteroaryl ring form a fused cycloalkyl ring, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

19. The compound of any of claims **1-12**, wherein R^{9a} is H and R^{9b} is selected from H, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with 1 to 3 fluoro groups, cycloalkyl optionally substituted with lower alkyl or one to three fluoro, cycloalkylalkyl optionally substituted with lower alkyl or one to three fluoro substituents, heterocycloalkyl optionally substituted with lower alkyl, heterocycloalkylalkyl, arylalkyl optionally substituted with from 1 to 3 members selected from lower alkyl, fluoro or haloalkyl and heteroarylalkyl optionally substituted with from one to three members selected from alkyl, fluoro or haloalkyl.

20. The compound of claim **19**, wherein R^{9a} is H and R^{9b} is selected from (i) H, methyl, ethyl, t-butyl, propyl, isopropyl, 2-butyl, n-butyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 3-

methoxypropyl, 2,2,2-trifluoroethyl, or 4-methoxybutyl and (ii) cyclopropyl, cyclobutyl, cyclopentyl, cylohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexymethyl, benzyl, 1-methylbenzyl, 4,4-difluorocyclohexyl, 2-tetrahydrofuranylmethyl, 4-piperadinyl, 3-pyridyl, 2-pyridyl or 4-pyridyl,each of which is optionally substituted with from 1 to 3 members selected from lower alkyl, lower alkoxy, fluoro or CF_3, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

21. The compound of any of claims **1-12** , wherein -N(R^{9a})(R^{9b}) is 1-piperadinyl, 4-morpholinyl, 1-piperazinyl or 1-pyrrolidinyl, each of which is optionally substituted with one to three members selected from lower alkyl, haloalkyl, lower alkoxy or fluoro, or a salt, a prodrug, a solvate, a tautomer, or a stereoisomer thereof.

22. The compound according to claim **1**, wherein the compound is selected from any of compounds P-3001, P-3003 to P-3053, P-4001 to P-4032 and P-4036 to P-4202 as set forth in Table 1 or Table 2 , or a salt, a prodrug, a solvate, a tautomer, or a stereoisomer thereof.

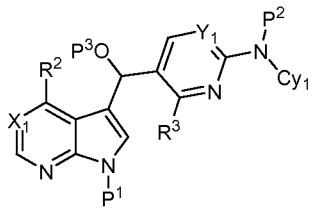
23. A composition comprising a compound according to any of claims **1-22**, or a salt, a prodrug, a solvate, a tautomer, or a stereoisomer thereof; and a pharmaceutically acceptable carrier.

24. A composition comprising a compound of any of claims **1-22**, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof, a pharmaceutically acceptable carrier and a chemotherapeutic agent.

25. A kit comprising a compound according to any of claims **1-22**, or a salt, a prodrug, a solvate, a tautomer or a stereoisomer thereof.

26. A method for preparing a compound of Formula I according to claim **1**, said method comprising:

contacting a compound of Formula (II):



(II)

with an agent under conditions sufficient to prepare the compound of Formula (I), wherein P^1 and P^2 are each independently an amino protecting group and P^3 is H or a protecting group.

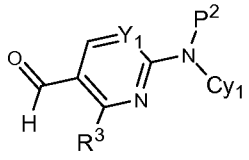
27. A method for preparing a compound of Formula II according to claim **26**, said method comprising:

contacting a compound of Formula (III):



(III)

with a compound of Formula IV:



IV

under conditions sufficient to form a compound of Formula (II), wherein Z^2 is Cl, Br or R^2 and Z^3 is iodo or a leaving group.

28. A method for treating a subject suffering from or at risk of a disease or condition, comprising administering to the subject in need thereof an effective amount of a compound according to any of claims **1-22**, wherein the disease or condition is selected from the group consisting of rheumatoid arthiritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, systemic sclerosis, demyelinating disorders, multiple sclerosis, Charcot Marie Tooth syndrome, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, ulcerative colitis, Crohn's disease, immune thrombocytopenic purpura, atherosclerosis, systemic lupus erythematosis, myelopreparation for autologous transplantation, transplant rejection, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, renal hypertrophy, type I diabetes, acute pain, inflammatory pain, neuropathic pain, acute myeloid leukemia, melanoma, multiple myeloma, breast cancer, prostate cancer, pancreatic cancer, lung cancer, ovarian cancer, gliomas, glioblastomas, neurofibromatosis, osteolytic bone metastases, brain metastases, gastrointestinal stromal tumors, and giant cell tumors.

29. A method for treating a subject suffering from or at risk of a disease or condition, comprising administering to the subject in need thereof an effective amount of a compound according to any of claims **1-22**, wherein the disease or condition is selected from the group consisting of rheumatoid arthiritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, multiple sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, renal hypertrophy, acute myeloid leukemia, melanoma, multiple myeloma, breast cancer, prostate cancer, pancreatic cancer, glioblastoma, neurofibromatosis, brain metastases, and gastrointestinal stromal tumors.

30. A method for treating a subject suffering from or at risk of a disease or condition, comprising administering to the subject in need thereof an effective amount of a compound according to any of claims **1-22**, wherein the disease or condition is selected from the group consisting of pancreatic cancer, prostate cancer, and multiple myeloma.

31. Use of a compound according to any of claims **1-22** in the preparation of a medicament for the treatment of a disease or condition selected from the group consisting of rheumatoid arthiritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, systemic sclerosis, demyelinating disorders, multiple sclerosis, Charcot Marie Tooth syndrome, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, ulcerative colitis, Crohn's disease, immune thrombocytopenic purpura, atherosclerosis, systemic lupus erythematosis, myelopreparation for autologous transplantation, transplant rejection, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, renal hypertrophy, type I diabetes, acute pain, inflammatory pain, neuropathic pain, acute myeloid leukemia, melanoma, multiple myeloma, breast cancer, prostate cancer, pancreatic cancer, lung cancer, ovarian cancer, gliomas, glioblastomas, neurofibromatosis, osteolytic bone metastases, brain metastases, gastrointestinal stromal tumors, and giant cell tumors.

32. Use of a compound according to any of claims **1-22** in the preparation of a medicament for the treatment of a disease or condition selected from the group consisting of rheumatoid arthiritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, multiple sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, renal hypertrophy, acute myeloid leukemia, melanoma, multiple myeloma, breast cancer, prostate cancer, pancreatic cancer, glioblastoma, neurofibromatosis, brain metastases, and gastrointestinal stromal tumors.

33. Use of a compound according to any of claims **1-22** in the preparation of a medicament for the treatment of a disease or condition selected from the group consisting of pancreatic cancer, prostate cancer, and multiple myeloma.

34. A compound according to any of claims **1-22** for the treatment of a disease or condition selected from the group consisting of rheumatoid arthiritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, systemic sclerosis, demyelinating disorders, multiple sclerosis, Charcot Marie Tooth syndrome, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, ulcerative colitis, Crohn's disease, immune thrombocytopenic purpura, atherosclerosis, systemic lupus erythematosis, myelopreparation for autologous transplantation, transplant rejection, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, renal hypertrophy, type I diabetes, acute pain,

inflammatory pain, neuropathic pain, acute myeloid leukemia, melanoma, multiple myeloma, breast cancer, prostate cancer, pancreatic cancer, lung cancer, ovarian cancer, gliomas, glioblastomas, neurofibromatosis, osteolytic bone metastases, brain metastases, gastrointestinal stromal tumors, and giant cell tumors.

35. A compound according to any of claims **1-22** for the treatment of a disease or condition selected from the group consisting of rheumatoid arthiritis, osteoarthritis, osteoporosis, peri-prosthetic osteolysis, multiple sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, renal hypertrophy, acute myeloid leukemia, melanoma, multiple myeloma, breast cancer, prostate cancer, pancreatic cancer, glioblastoma, neurofibromatosis, brain metastases, and gastrointestinal stromal tumors.

36. A compound according to any of claims **1-22** for the treatment of a disease or condition selected from the group consisting of pancreatic cancer, prostate cancer, and multiple myeloma.

COMPUESTOS Y MÉTODOS PARA LA MODULACIÓN DE QUINASA E INDICACIONES DE LA MISMA

CAMPO DE LA INVENCIÓN

[0001] Se divulgan los compuestos novedosos y usos de los mismos. En ciertas formas de realización divulgadas los compuestos son inhibidores de quinasa.

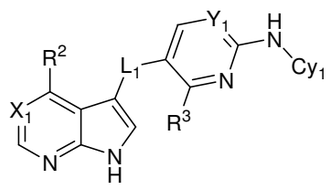
RESUMEN DE LA INVENCIÓN

[0002] En ciertos aspectos y formas de realización aquí descritas, se proporcionan los compuestos, así como varias sales, formulas, conjugados, derivados, formas y usos de los mismos. En ciertas formas de realización, los compuestos están activos en una o más proteínas quinasas, incluyendo los tipos Fms, Kit, Flt3, TrkA, TrkB y/o TrkC, lo que incluye cualquier mutación de éstas. En ciertas formas de realización, los compuestos están activos en la quinasa tipo Fms. En ciertas formas de realización, los compuestos están activos en las quinasas tipo Fms y Kit. En ciertas formas de realización, los compuestos están activos de forma selectiva en la quinasa Fms relativa a la quinasa Kit. En ciertas formas de realización, los compuestos están activos en las quinasas tipo Fms y Flt3. En ciertas formas de realización, los compuestos están activos en la quinasa tipo Fms y una o más quinasas tipos TrkA, TrkB y TrkC.

[0003] De acuerdo con la presente invención se contemplan además los métodos de uso de los compuestos al tratar enfermedades y condiciones asociadas con la regulación de la actividad de una o más Fms, Kit, Flt3, TrkA, TrkB y TrkC, incluyendo cualquier mutación de éstas. De este modo, se proporciona el uso de los compuestos para los métodos terapéuticos que involucran la modulación de la proteína quinasa. En ciertas formas de realización, se usan los compuestos para métodos terapéuticos que involucran el tratamiento de distintas indicaciones,

incluyendo, pero no limitadas a artritis reumatoide, osteoartritis, osteoporosis, osteolisis periprotésica, esclerosis sistémica, desórdenes desmielinizantes, esclerosis múltiple, Síndrome de Charcot Marie Tooth, esclerosis amiotrófica lateral, Enfermedad de Alzheimer, Enfermedad de Parkinson, isquemia global, colitis ulcerativa, Enfermedad de Crohn, púrpura trombocitopénica inmune, arterioesclerosis, lupus eritematoso sistémico, mielopreparación para trasplante autólogo, rechazo de trasplante, glomerulonefritis, nefritis intersticial, Nefritis lúpica, necrosis renal tubular, nefropatía diabética, hipertrofía renal, diabetes tipo I, dolor agudo, dolor inflamatorio, dolor neuropático, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de seno, cáncer de próstata, cáncer de páncreas, cáncer de pulmón, cáncer de ovario, gliomas, glioblastoma, neurofibromatosis, metástasis ósea, metástasis Cerebral, tumores estromales gastrointestinales y tumores de células gigantes. En algunas formas de realización, los compuestos son los descritos en la Fórmula I descrita más adelante.

[0004] En un primer aspecto, se proporcionan compuestos que tienen la estructura de acuerdo con la siguiente Fórmula I:



Fórmula I o una sal, un profármaco, un solvato, un tautómero o un estereoisómero del mismo, donde:

X_1 es –N=, -C(H)=, o -C(R^1)= ;

Y_1 es –N= y R^3 es hidrógeno; o Y_1 es -C(H)= y R^3 es flúor o cloro;

L_1 es -C(H_2)- o -C(O)-;

Cy_1 es cicloalquil sustituido opcionalmente con una o más R^4, fenil sustituido opcionalmente con una o más R^5, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^6 y sustituido opcionalmente en un átomo de nitrógeno disponible con R^7;

Donde X_1 es $-C(R^1)=$, R^2 es hidrógeno;

Donde X_1 es –N= o -C(H)=, R^2 se selecciona de un grupo que consiste de hidrógeno, cicloalquil, alquil inferior opcionalmente independientemente sustituido con una o más R^8, $-N(R^{9a})(R^{9b})$, y $-O-R^9$;

R^1 es flúor, cloro, o alquil inferior sustituido opcionalmente con una o más flúor;

Cada R^4 se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor;

Cada R^5 se selecciona independientemente del grupo que consiste de flúor, cloro, $-O-R^{10}$, $-S-R^{11}$, $-S(O_2)-R^{12}$, y alquil inferior sustituido opcionalmente con una o más R^{13};

Cada R^6 se selecciona independientemente del grupo que consiste de flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor; o dos R^6 unidos a los átomos de carbono adyacentes al anillo, tomados juntos, forman un anillo de cicloalquil combinado;

R^7 es cicloalquil, alcoxi inferior o alquil inferior sustituido opcionalmente con uno o más flúor;

R^8 es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{9a} es H y R^{9b} se seleccionan del grupo que consiste de (i) H, alquil inferior, alquil inferior sustituido con uno o más flúor, alquil inferior sustituido con

alcoxi inferior o alquil inferior sustituido con hidroxilo y (ii) cicloalquil, cicloalquilalquil, heterocicloalquil, heterocicloalquilalquil, ariloalquil, heteroariloalquil, cada uno de los cuales se sustituye opcionalmente con uno a tres miembros seleccionados del alquil inferior, haloalquil, alcoxi inferior o flúor; o

R^{9a} y R^{9b} junto con el nitrógeno al que se unen forma un anillo de 5- o 6-miembros que tiene de 0 a 1 heteroátomo adicional seleccionado de O, N o S, cada uno de los cuales se sustituye opcionalmente con uno a tres miembros seleccionados del alquil inferior, haloalquil, alcoxi inferior o flúor;

R^9 es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior;

Cada R^{10}, R^{11} y R^{12} es independientemente alquil inferior sustituido opcionalmente con uno o más flúor; y

Cada R^{13} se selecciona independientemente del grupo que consiste de flúor, -OH, y alcoxi inferior sustituido opcionalmente con uno o más flúor.

En algunas formas de realización de los compuestos de la Fórmula I, R^3 es flúor. En ciertas formas de realización la sal es una sal farmacéuticamente aceptable.

[0005] En algunas formas de realización, la invención suministra los compuestos de la fórmula I o cualquiera de las subfórmulas como se describe aquí, o una sal farmacéuticamente aceptable, un solvato, un tautómero o un estereoisómero del mismo. En otras formas de realización de la invención suministra un compuesto de la fórmula I o cualquiera de las subfórmulas como se describe aquí, o una sal farmacéuticamente aceptable o un solvato del mismo. En algunas formas de realización, el solvato es un hidrato.

[0006] En algunas formas de realización de compuestos de la Fórmula I, X_1 es –N= y R^2 se selecciona del grupo que consiste de cicloalquil, alquil inferior sustituido opcionalmente con una o más R^8, por ejemplo, 1 a 3 R^8, y -O-R^9. En una forma de realización, X_1 es –N= y R^2 se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, X_1 es –N= y R^2 se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, X_1 es -N= y R^2 se selecciona del grupo que consiste de metil, ciclopropil, ciclobutil, ciclopentil, ciclohexil, metoxi, etoxi, y 2-metoxi-etoxi.

[0007] En algunas formas de realización de compuestos de la Fórmula I, X_1 es -C(H)= o -C(R^1)= y R^1 es flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor. En una de las formas de realización, X_1 es -C(H)= o -C(R^1)= y R^1 es cloro o alquil inferior. En una de las formas de realización, X_1 es -C(H)= o -C(R^1)= y R^1 es cloro o C_{1-3} alquil. En una de las formas de realización, X_1 es -C(H)= o -C(R^1)= y R^1 es cloro o metil.

[0008] En algunas formas de realización de compuestos de la Fórmula I, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula I, Cy_1 es cicloalquil sustituido opcionalmente con una o más R^4, fenil sustituido opcionalmente con una o más R^5, o 5 o 6 miembros heteroarilo sustituido opcionalmente en un átomo de carbono disponible con una o más R^6 y sustituido opcionalmente en un átomo de nitrógeno disponible con R^7, donde cicloalquil es ciclopropil, ciclobutil, ciclopentil, ciclohexil o cicloheptil y heteroarilo es piridinil o pirazolil.

[0009] En algunas formas de realización de compuestos de la Fórmula I, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula I, Cy_1 es cicloalquil sustituido opcionalmente con una o más R^4, fenil sustituido opcionalmente con una o más R^5, o 5 o 6 miembros heteroarilo sustituido opcionalmente en un átomo de carbono disponible con una o más R^6 y sustituido opcionalmente en un átomo de nitrógeno disponible con R^7, donde cicloalquil es ciclohexil, o cicloheptil y heteroarilo es piridina-3-il o pirazol-4-il.

[0010] En algunas formas de realización de compuestos de la Fórmula I, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula I, L_1 es $-C(H_2)-$. En algunas formas de realización de compuestos de la Fórmula I, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula I, L_1 es -C(O)-.

[0011] En algunas formas de realización de compuestos de la Fórmula I, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula I, Y_1 es –N= y R^3 es hidrógeno. En algunas formas de realización de compuestos de la Fórmula I, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula I, Y_1 es -C(H)= y R^3 es flúor.

[0012] En algunas formas de realización de los compuestos (A) de la Fórmula I, X_1 es N y todas las otras variables son las definidas aquí. Dentro de algunas formas de realización dentro de las formas de realización (A), L_1 es CH_2, Y_1 es CH y R^3 es F. En otros casos, L_1 es CH_2, Y_1 es N y R^3 es F. En otros casos, L_1 es -C(=O)-, Y_1 es CH y R^3 es F. Incluso en otros casos, L_1 es -C(=O)-, Y_1 es N y R^3 es F.

[0013] En algunas formas de realización de los compuestos (B) de la Fórmula I, X_1 es $–C(R^1)=$, R^1 y todas las otras variables son las definidas aquí. Dentro de las formas de realización (B), en ciertas instancias, L_1 es CH_2, Y_1 es CH y R^3 es F. En

otras instancias L_1 es -C(=O)-, Y_1 es CH y R^3 es F. En otros casos, L_1 es $–CH_2$-, Y_1 es N y R^3 es F. Incluso en otros casos, L_1 es -C(=O)-, Y_1 es N y R^3 es F.

[0014] En algunas formas de realización de los compuestos (C) de la Fórmula I, X_1 es N, R^2 es $-N(R^{9a})(R^{9b})$, y todas las otras variables son las definidas aquí.

[0015] En algunas formas de realización de compuestos de la Fórmula I, Cy_1 es cicloalquil sustituido opcionalmente con una o más R^4. En ciertos casos, Cy_1 es ciclopropil, ciclobutil, ciclopentil, ciclohexil, ciclopentil, cada uno de los cuales es sustituido opcionalmente con de 1 a 3 R^4. Todas las otras variables son las definidas aquí.

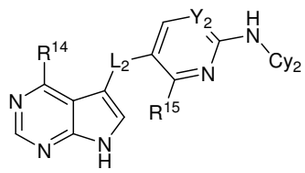
[0016] En algunas formas de realización de compuestos de la Fórmula I, Cy_1 es fenil sustituido opcionalmente con una o más R^5 y todas las otras variables son las definidas aquí.

[0017] En algunas formas de realización de compuestos de la Fórmula I, done Cy_1 es heteroarilo de 5 o 6-miembros sustituido opcionalmente con un átomo de carbono disponibles con una o más R^6 y sustituido opcionalmente con un átomo de nitrógeno disponible con R^7. En ciertos casos, Cy_1 es 3-piridil, 2-pyrrolyl, 3-pyrrolyl o 4-pirazolil, sustituido opcionalmente en un átomo de carbono disponible con de 1 a 3 R^6 y sustituido opcionalmente en un átomo de nitrógeno disponible con R^7. En algunas formas de realización, cada R^6 se selecciona independientemente del grupo que consiste de flúor, cloro, bromo, cicloalquil, alquil inferior sustituidos opcionalmente con uno a tres flúores y alcoxi inferior sustituido opcionalmente con no a tres flúores; o dos R^6 unidos a los átomos de carbono adyacentes al anillo heteroaril forman un anillo cicloalquil fusionado. Todas las otras variables son las definidas aquí.

[0018] En algunas formas de realización de compuestos de la Fórmula I, R^{9a} es H y R^{9b} se selecciona del H, alquil inferior, alquil inferior sustituido con hidroxi, alquil inferior sustituido con alcoxi inferior, alquil inferior sustituido con 1 a 3 grupos de flúor, cicloalquil sustituido opcionalmente con alquil inferior o uno a tres flúor, cicloalquilalquil sustituido opcionalmente con alquil inferior o uno a tres flúor sustituyentes, heterocicloalquil sustituido opcionalmente con alquil inferior, heterocicloalquilalquil, ariloalquil sustituido opcionalmente con de 1 a 3 miembros seleccionados del alquil inferior, flúor o haloalquil y heteroariloalquil sustituido opcionalmente con de uno a tres miembros seleccionados del alquil, flúor o haloalquil. En ciertos casos, R^{9a} es H y R^{9b} se selecciona del (i) H, metil, etil, t-butil, propilo, isopropilo, 2-butil, n-butil, 2-hidroxi-2-metilpropilo, 2-metoxietil, 3-metoxipropilo, 2,2,2-trifluoroetil, o 4-metoxibutil y (ii) ciclopropil, ciclobutil, ciclopentil, cilohexil, ciclopropilmetil, ciclobutilmetil, ciclopentilmetil, cicloheximetil, bencil, 1-metilbencil, 4,4-difluorociclohexil, 2-tetrahidrofuranilmetil, 4-piperadinil, 3-piridil, 2-piridil o 4-piridil, cada uno de los cuales se sustituye opcionalmente con de 1 a 3 miembros seleccionados del alquil inferior, alcoxi inferior, flúor o CF_3. Todas las otras variables son las definidas aquí.

[0019] En algunas formas de realización de compuestos de la Fórmula I, $-N(R^{9a})(R^{9b})$ es 1-piperadinil, 4-morfolinil, 1-piperazinil o 1-pirrolidinil, cada uno de los cuales se sustituye opcionalmente con uno a tres miembros seleccionados del alquil inferior, haloalquil, alcoxi inferior o flúor. Todas las otras variables son las definidas aquí.

[0020] En un segundo aspecto, se proporcionan compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ia:



Fórmula Ia

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Y_2 es –N= y R^{15} es hidrógeno; o Y_2 es -C(H)= y R^{15} es flúor o cloro;

L_2 es -$C(H_2)$- o -C(O)-;

Cy_2 es cicloalquil sustituido opcionalmente con una o más R^{16}, fenil sustituido opcionalmente con una o más R^{17}, o heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{18} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{19};

R^{14} se selecciona del grupo que consiste de cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{20}, -$N(R^{9a})(R^{9b})$, y -O-R^{21};

Cada R^{16} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor;

Cada R^{17} se selecciona independientemente del grupo que consiste de flúor, cloro, -O-R^{22}, -S-R^{23}, -S(O_2)-R^{24}, y alquil inferior sustituido opcionalmente con una o más R^{25};

Cada R^{18} se selecciona independientemente del grupo que consiste de flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor; o dos R^{18} unidos a los átomos de carbono adyacentes del anillo de heteroarilo, tomados juntos, forman un anillo de cicloalquil combinado;

R^{19} es cicloalquil, alcoxi inferior, o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{20} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{21} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior;

Cada R^{22}, R^{23} y R^{24} son independientemente un alquil inferior sustituido opcionalmente con uno o más flúor; y

Cada R^{25} se selecciona independientemente del grupo que consiste de flúor, -OH, y alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0021] En algunas formas de realización de compuestos de la Fórmula Ia, R^{14} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{14} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{14} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

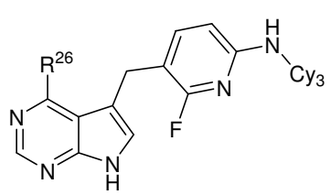
[0022] En algunas formas de realización de compuestos de la Fórmula Ia, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ia, Cy_2 es cicloalquil sustituido opcionalmente con una o más R^{16}, fenil sustituido opcionalmente con una o más R^{17}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{18} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{19}, donde cicloalquil es ciclopropil, ciclobutil, ciclopentil, ciclohexil, o cicloheptil y heteroarilo es piridinil o pirazolil.

[0023] En algunas formas de realización de compuestos de la Fórmula Ia, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ia, Cy_2 es cicloalquil sustituido opcionalmente con una o más R^{16}, fenil sustituido opcionalmente con una o más R^{17}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{18} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{19}, donde cicloalquil es ciclohexil, o cicloheptil y heteroarilo es piridina-3-il o pirazol-4-il.

[0024] En algunas formas de realización de compuestos de la Fórmula Ia, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ia, L_2 es -C(H_2)-. En algunas formas de realización de compuestos de la Fórmula Ia, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ia, L_2 es -C(O)-.

[0025] En algunas formas de realización de compuestos de la Fórmula Ia, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ia, Y_2 es –N= y R^{15} es hidrógeno. En algunas formas de realización de compuestos de la Fórmula Ia, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ia, Y_2 es -C(H)= y R^{15} es flúor.

[0026] En un tercer aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ib:



Fórmula Ib

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Cy_3 es cicloalquil sustituido opcionalmente con una o más R^{27}, fenil sustituido opcionalmente con una o más R^{28}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{29} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{30};

R^{26} se selecciona del grupo que consiste de cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{31}, y -O-R^{32};

Cada R^{27} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor;

Cada R^{28} se selecciona independientemente del grupo que consiste de flúor, cloro, -O-R^{33}, -S-R^{34}, -S(O_2)-R^{35}, y alquil inferior sustituido opcionalmente con una o más R^{36};

Cada R^{29} se selecciona independientemente del grupo que consiste de flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor y alcoxi inferior sustituido opcionalmente con uno o más flúor; o dos R^{29} unidos a los átomos de carbono adyacentes del anillo de heteroarilo, tomados juntos, forman un anillo de cicloalquil combinado;

R^{30} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{31} i flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{32} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior;

Cada R^{33}, R^{34} y R^{35} son independientemente un alquil inferior sustituido opcionalmente con uno o más flúor; y

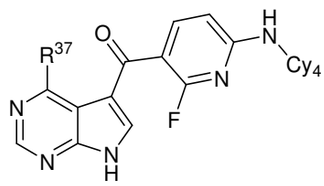
Cada R^{36} se selecciona independientemente del grupo que consiste de flúor, -OH, y alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0027] En algunas formas de realización de compuestos de la Fórmula Ib, R^{26} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{26} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{26} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

[0028] En algunas formas de realización de compuestos de la Fórmula Ib, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ib, Cy_3 es cicloalquil sustituido opcionalmente con una o más R^{27}, fenil sustituido opcionalmente con una o más R^{28}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{29} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{30}, donde cicloalquil es ciclopropil, ciclobutil, ciclopentil, ciclohexil o cicloheptil y heteroarilo es piridinil o pirazolil.

[0029] En algunas formas de realización de compuestos de la Fórmula Ib, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ib, Cy_3 es cicloalquil sustituido opcionalmente con una o más R^{27}, fenil sustituido opcionalmente con una o más R^{28}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{29} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{30}, donde cicloalquil es ciclohexil o cicloheptil y heteroarilo es piridina-3-il o pirazol-4-il.

[0030] En un cuarto aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ic:



Fórmula Ic

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Cy_4 es cicloalquil sustituido opcionalmente con una o más R^{38}, fenil sustituido opcionalmente con una o más R^{39}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{40} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{41};

R^{37} se selecciona del grupo que consiste de cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{42}, y -O-R^{43};

Cada R^{38} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor;

Cada R^{39} se selecciona independientemente del grupo que consiste de flúor, cloro, -O-R^{44}, -S-R^{45}, -S(O_2)-R^{46}, y alquil inferior sustituido opcionalmente con una o más R^{47};

Cada R^{40} se selecciona independientemente del grupo que consiste de flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor y alcoxi inferior sustituido opcionalmente con uno o más flúor; o dos R^{40} unidos a los átomos de carbono adyacentes del anillo de heteroarilo, tomados juntos, forman un anillo de cicloalquil combinado;

R^{41} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{42} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{43} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior;

Cada R^{44}, R^{45} y R^{46} son independientemente un alquil inferior sustituido opcionalmente con uno o más flúor; y

Cada R^{47} se selecciona independientemente del grupo que consiste de flúor, -OH, y alcoxi inferior sustituido opcionalmente con uno o más flúor.

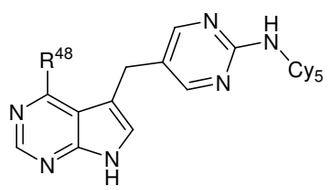
[0031] En algunas formas de realización de compuestos de la Fórmula Ic, R^{37} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{37} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{37} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi, y 2-metoxi-etoxi.

[0032] En algunas formas de realización de compuestos de la Fórmula Ic, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ic, Cy_4 es cicloalquil sustituido opcionalmente con una o más R^{38}, fenil sustituido opcionalmente con una o más R^{39}, heteroarilo de 5 o 6 miembros sustituidos opcionalmente en un átomo de carbono disponible con una o más R^{40} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{41}, donde cicloalquil es ciclopropil, ciclobutil, ciclopentil, ciclohexil o cicloheptil y heteroarilo es piridinil o pirazolil.

[0033] En algunas formas de realización de compuestos de la Fórmula Ic, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ic, Cy_4 es cicloalquil sustituido opcionalmente con una o más R^{38}, fenil sustituido opcionalmente con una o más R^{39}, heteroarilo de 5 o 6 miembros sustituido

opcionalmente en un átomo de carbono disponible con una o más R^{40} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{41}, donde cicloalquil es ciclohexil o cicloheptil y heteroarilo es piridina-3-il o pirazol-4-il.

[0034] En un quinto aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Id:



Fórmula Id

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Cy_5 es cicloalquil sustituido opcionalmente con una o más R^{49}, fenil sustituido opcionalmente con una o más R^{50}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{51} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{52};

R^{48} se selecciona del grupo que consiste de cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{53}, y -O-R^{54};

Cada R^{49} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor;

Cada R^{50} se selecciona independientemente del grupo que consiste de flúor, cloro, -O-R^{55}, -S-R^{56}, -S(O_2)-R^{57}, y alquil inferior sustituido opcionalmente con una o más R^{58};

Cada R^{51} se selecciona independientemente del grupo que consiste de flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor; o

dos R^{51} unidos a los átomos de carbono adyacentes del anillo de heteroarilo, tomados juntos, forman un anillo de cicloalquil combinado;

R^{52} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{53} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{54} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior;

Cada R^{55}, R^{56} y R^{57} son independientemente un alquil inferior sustituido opcionalmente con uno o más flúor; y

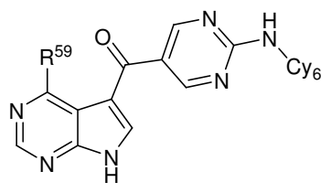
Cada R^{58} se selecciona independientemente del grupo que consiste de flúor, -OH, y alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0035] En algunas formas de realización de compuestos de la Fórmula Id, R^{48} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{48} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{48} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi, y 2-metoxi-etoxi.

[0036] En algunas formas de realización de compuestos de la Fórmula Id, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Id, Cy_5 es cicloalquil sustituido opcionalmente con una o más R^{49}, fenil sustituido opcionalmente con una o más R^{50}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{51} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{52}, donde cicloalquil es ciclopropil, ciclobutil, ciclopentil, ciclohexil o cicloheptil y heteroarilo es piridinil o pirazolil.

[0037] En algunas formas de realización de compuestos de la Fórmula Id, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Id, Cy_5 es cicloalquil sustituido opcionalmente con una o más R^{49}, fenil sustituido opcionalmente con una o más R^{50}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{51} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{52}, donde cicloalquil es ciclohexil o cicloheptil y heteroarilo es piridina-3-il o pirazol-4-il.

[0038] En un sexto asepcto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ie:



Fórmula Ie

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Cy_6 es cicloalquil sustituido opcionalmente con una o más R^{60}, fenil sustituido opcionalmente con una o más R^{61}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{62} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{63};

R^{59} se selecciona del grupo que consiste de cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{64}, y -O-R^{65};

Cada R^{60} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor;

Cada R^{61} se selecciona independientemente del grupo que consiste de flúor, cloro, -O-R^{66}, -S-R^{67}, -S(O_2)-R^{68}, y alquil inferior sustituido opcionalmente con una o más R^{69};

Cada R^{62} se selecciona independientemente del grupo que consiste de flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor; o dos R^{62} unidos a los átomos de carbono adyacentes del anillo de heteroarilo, tomados juntos, forman un anillo de cicloalquil combinado;

R^{63} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{64} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{65} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior;

Cada R^{66}, R^{67} y R^{68} son independientemente un alquil inferior sustituido opcionalmente con uno o más flúor; y

Cada R^{69} se selecciona independientemente del grupo que consiste de flúor, -OH, y alcoxi inferior sustituido opcionalmente con uno o más flúor.

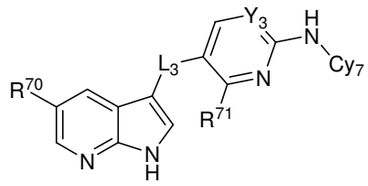
[0039] En algunas formas de realización de compuestos de la Fórmula Ie, R^{59} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{59} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{59} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi, y 2-metoxi-etoxi.

[0040] En algunas formas de realización de compuestos de la Fórmula Ie, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Ie, Cy_6 es cicloalquil sustituido opcionalmente con una o más R^{60}, fenil sustituido opcionalmente con una o más R^{61}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{62} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{63}, donde cicloalquil es ciclopropil, ciclobutil, ciclopentil, ciclohexil o cicloheptil y heteroarilo es piridinil o pirazolil.

[0041] En algunas formas de realización de compuestos de la Fórmula Ie, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ie, Cy_6 es cicloalquil sustituido opcionalmente con una o más R^{60}, fenil sustituido opcionalmente con una o más R^{61}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{62} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{63}, donde cicloalquil es ciclohexil o cicloheptil y heteroarilo es piridina-3-il o pirazol-4-il.

[0042] En un séptimo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula If:



Fórmula If

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Y_3 es –N= y R^{71} es hidrógeno; o Y_3 es -C(H)= y R^{71} es flúor;

L_3 es $-C(H_2)-$ o -C(O)-;

Cy_7 es cicloalquil sustituido opcionalmente con una o más R^{72}, fenil sustituido opcionalmente con una o más R^{73}, heteroarilo de 5 o 6 miembros sustituido

opcionalmente en un átomo de carbono disponible con una o más R^{74} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{75};

R^{70} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

Cada R^{72} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor;

Cada R^{73} se selecciona independientemente del grupo que consiste de flúor, cloro, -O-R^{76}, -S-R^{77}, -S(O_2)-R^{78}, y alquil inferior sustituido opcionalmente con una o más R^{79};

Cada R^{74} se selecciona independientemente del grupo que consiste de flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor y alcoxi inferior sustituido opcionalmente con uno o más flúor; o dos R^{74} unidos a los átomos de carbono adyacentes del anillo de heteroarilo, tomados juntos, forman un anillo de cicloalquil combinado;

R^{75} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor;

Cada R^{76}, R^{77} y R^{78} son independientemente un alquil inferior sustituido opcionalmente con uno o más flúor; y

Cada R^{79} se selecciona independientemente del grupo que consiste de flúor, -OH, y alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0043] En algunas formas de realización de compuestos de la Fórmula If, R^{70} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{70} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{70} es hidrógeno, cloro o metil.

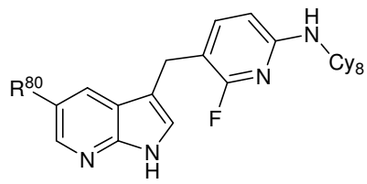
[0044] En algunas formas de realización de compuestos de la Fórmula If, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula If, Cy_7 es cicloalquil sustituido opcionalmente con una o más R^{72}, fenil sustituido opcionalmente con una o más R^{73}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{74} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{75}, donde cicloalquil es ciclopropil, ciclobutil, ciclopentil, ciclohexil o cicloheptil y heteroarilo es piridinil o pirazolil.

[0045] En algunas formas de realización de compuestos de la Fórmula If, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula If, Cy_7 es cicloalquil sustituido opcionalmente con una o más R^{72}, fenil sustituido opcionalmente con una o más R^{73}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{74} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{75}, donde cicloalquil es ciclohexil o cicloheptil y heteroarilo es piridina-3-il o pirazol-4-il.

[0046] En algunas formas de realización de compuestos de la Fórmula If, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula If, L_3 es $-C(H_2)-$. En algunas formas de realización de compuestos de la Fórmula If, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula If, L_3 es -C(O)-.

[0047] En algunas formas de realización de compuestos de la Fórmula If, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula If, Y_3 es –N= y R^{71} es hidrógeno. En algunas formas de realización de compuestos de la Fórmula If, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula If, Y_3 es -C(H)= y R^{71} es flúor.

[0048] En un octavo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ig:



Fórmula Ig

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Cy_8 es cicloalquil sustituido opcionalmente con una o más R^{81}, fenil sustituido opcionalmente con una o más R^{82}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{83} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{84};

R^{80} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

Cada R^{81} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor;

Cada R^{82} se selecciona independientemente del grupo que consiste de flúor, cloro, -O-R^{85}, -S-R^{86}, -S(O_2)-R^{87}, y alquil inferior sustituido opcionalmente con una o más R^{88};

Cada R^{83} se selecciona independientemente del grupo que consiste de flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor; o dos R^{83} unidos a los átomos de carbono adyacentes del anillo de heteroarilo, tomados juntos, forman un anillo de cicloalquil combinado;

R^{84} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor;

Cada R^{85}, R^{86} y R^{87} son independientemente un alquil inferior sustituido opcionalmente con uno o más flúor; y

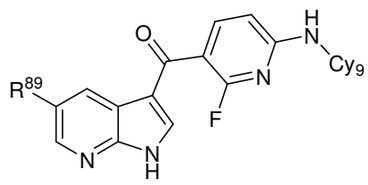
Cada R^{88} se selecciona independientemente del grupo que consiste de flúor, -OH, y alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0049] En algunas formas de realización de compuestos de la Fórmula Ig, R^{80} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{80} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{80} es hidrógeno, cloro o metil.

[0050] En algunas formas de realización de compuestos de la Fórmula Ig, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ig, Cy_8 es cicloalquil sustituido opcionalmente con una o más R^{81}, fenil sustituido opcionalmente con una o más R^{82}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{83} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{84}, donde cicloalquil es ciclopropil, ciclobutil, ciclopentil, ciclohexil o cicloheptil y heteroarilo es piridinil o pirazolil.

[0051] En algunas formas de realización de compuestos de la Fórmula Ig, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ig, Cy_8 es cicloalquil sustituido opcionalmente con una o más R^{81}, fenil sustituido opcionalmente con una o más R^{82}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{83} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{84}, donde cicloalquil es ciclohexil o cicloheptil y heteroarilo es piridina-3-il o pirazol-4-il.

[0052] En un noveno aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ih:



Fórmula Ih

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Cy_9 es cicloalquil sustituido opcionalmente con una o más R^{90}, fenil sustituido opcionalmente con una o más R^{91}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{92} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{93};

R^{89} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

Cada R^{90} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor;

Cada R^{91} se selecciona independientemente del grupo que consiste de flúor, cloro, -O-R^{94}, -S-R^{95}, -S(O_2)-R^{96}, y alquil inferior sustituido opcionalmente con una o más R^{97};

Cada R^{92} se selecciona independientemente del grupo que consiste de flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor; o dos R^{92} unidos a los átomos de carbono adyacentes del anillo de heteroarilo, tomados juntos, forman un anillo de cicloalquil combinado;

R^{93} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor;

Cada R^{94}, R^{95} y R^{96} son independientemente un alquil inferior sustituido opcionalmente con uno o más flúor; y

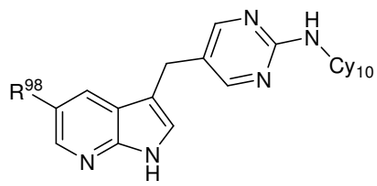
Cada R^{97} se selecciona independientemente del grupo que consiste de flúor, -OH, y alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0053] En algunas formas de realización de compuestos de la Fórmula Ih, R^{89} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{89} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{89} es hidrógeno, cloro o metil.

[0054] En algunas formas de realización de compuestos de la Fórmula Ih, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ih, Cy_9 es cicloalquil sustituido opcionalmente con una o más R^{90}, fenil sustituido opcionalmente con una o más R^{91}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{92} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{93}, donde cicloalquil es ciclopropil, ciclobutil, ciclopentil, ciclohexil o cicloheptil y heteroarilo es piridinil o pirazolil.

[0055] En algunas formas de realización de compuestos de la Fórmula Ih, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ih, Cy_9 es cicloalquil sustituido opcionalmente con una o más R^{90}, fenil sustituido opcionalmente con una o más R^{91}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{92} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{93}, donde cicloalquil es ciclohexil o cicloheptil y heteroarilo es piridina-3-il o pirazol-4-il.

[0056] En un décimo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ii:



Fórmula Ii

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo,donde:

Cy_{10} es cicloalquil sustituido opcionalmente con una o más R^{99}, fenil sustituido opcionalmente con una o más R^{100}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{101} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{102};

R^{98} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

Cada R^{99} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor;

Cada R^{100} se selecciona independientemente del grupo que consiste de flúor, cloro, -O-R^{103}, -S-R^{104}, -S(O_2)-R^{105}, y alquil inferior sustituido opcionalmente con una o más R^{106};

Cada R^{101} se selecciona independientemente del grupo que consiste de flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor; o dos R^{101} unidos a los átomos de carbono adyacentes del anillo de heteroarilo, tomados juntos, forman un anillo de cicloalquil combinado;

R^{102} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor;

Cada R^{102}, R^{104} y R^{105} son independientemente un alquil inferior sustituido opcionalmente con uno o más flúor; y

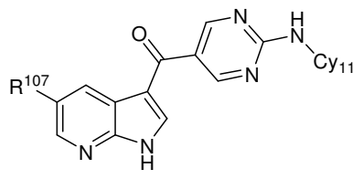
Cada R^{106} se selecciona independientemente del grupo que consiste de flúor, -OH, y alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0057] En algunas formas de realización de compuestos de la Fórmula Ii, R^{98} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{98} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{98} es hidrógeno, cloro o metil.

[0058] En algunas formas de realización de compuestos de la Fórmula Ii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ii, Cy_{10} es cicloalquil sustituido opcionalmente con una o más R^{99}, fenil sustituido opcionalmente con una o más R^{100}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{101} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{102}, donde cicloalquil es ciclopropil, ciclobutil, ciclopentil, ciclohexil o cicloheptil y heteroarilo es piridinil o pirazolil.

[0059] En algunas formas de realización de compuestos de la Fórmula Ii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ii, Cy_{10} es cicloalquil sustituido opcionalmente con una o más R^{99}, fenil sustituido opcionalmente con una o más R^{100}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{101} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{102}, donde cicloalquil es ciclohexil o cicloheptil y heteroarilo es piridina-3-il o pirazol-4-il.

[0060] En un onceavo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ij:



Fórmula Ij

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo,donde:

Cy_{11} es cicloalquil sustituido opcionalmente con una o más R^{108}, fenil sustituido opcionalmente con una o más R^{109}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{110} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{111};

R^{107} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

Cada R^{108} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor;

Cada R^{109} se selecciona independientemente del grupo que consiste de flúor, cloro, -O-R^{112}, -S-R^{113}, -S(O_2)-R^{114}, y alquil inferior sustituido opcionalmente con una o más R^{115};

Cada R^{110} se selecciona independientemente del grupo que consiste de flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor; o dos R^{110} unidos a los átomos de carbono adyacentes del anillo de heteroarilo, tomados juntos, forman un anillo de cicloalquil combinado;

R^{111} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor;

Cada R^{112}, R^{113} y R^{114} son independientemente un alquil inferior sustituido opcionalmente con uno o más flúor; y

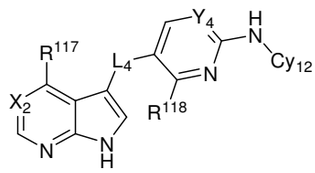
Cada R^{115} se selecciona independientemente del grupo que consiste de flúor, -OH, y alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0061] En algunas formas de realización de compuestos de la Fórmula Ij, R^{107} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{107} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{107} es hidrógeno, cloro o metil.

[0062] En algunas formas de realización de compuestos de la Fórmula Ij, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ij, Cy_{11} es cicloalquil sustituido opcionalmente con una o más R^{108}, fenil sustituido opcionalmente con una o más R^{109}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{110} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{111}, donde cicloalquil es ciclopropil, ciclobutil, ciclopentil, ciclohexil o cicloheptil y heteroarilo es piridinil o pirazolil.

[0063] En algunas formas de realización de compuestos de la Fórmula Ij, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ij, Cy_{11} es cicloalquil sustituido opcionalmente con una o más R^{108}, fenil sustituido opcionalmente con una o más R^{109}, heteroarilo de 5 o 6 miembros sustituido opcionalmente en un átomo de carbono disponible con una o más R^{110} y sustituido opcionalmente en un átomo de nitrógeno disponible con R^{111}, donde cicloalquil es ciclohexil o cicloheptil y heteroarilo es piridina-3-il o pirazol-4-il.

[0064] En un doceavo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ik:



Fórmula Ik

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

X_2 es –N=, -C(H)=, o -C(R^{116})= ;

Y_4 es –N= y R^{118} es hidrógeno; o Y_4 es -C(H)= y R^{118} es flúor;

L_4 es -C(H_2)- o -C(O)-;

Cy_{12} es cicloalquil sustituido opcionalmente con una o más R^{119};

Donde X_2 es -C(R^{116})=, R^{117} es hidrógeno;

Donde X_2 es –N= o -C(H)=, R^{117} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{120}, y -O-R^{121};

R^{116} es flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

Cada R^{119} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{120} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{121} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0065] En algunas formas de realización de compuestos de la Fórmula Ik, X_2 es –N= y R^{117} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{120}, y -O-R^{121}. En una de las formas de realización, X_2 es –N= y R^{117} se selecciona del grupo que consiste de

cicloalquil, alquil inferior, alcoxi inferior y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, X_2 es –N= y R^{117} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, X_2 es -N= y R^{117} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi, y 2-metoxi-etoxi.

[0066] En algunas formas de realización de compuestos de la Fórmula Ik, X_2 es -C(H)= o -C(R^{116})= y R^{116} es flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor. En una de las formas de realización, X_2 es -C(H)= o -C(R^{116})= y R^{116} es cloro o alquil inferior. En una de las formas de realización, X_2 es -C(H)= o -C(R^{116})= y R^{116} es cloro o C_{1-3} alquil. En una de las formas de realización, X_2 es -C(H)= o -C(R^{116})= y R^{116} es cloro o metil.

[0067] En algunas formas de realización de compuestos de la Fórmula Ik, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ik, Cy_{12} es ciclopentil sustituido opcionalmente con 1 o 2 R^{119}, ciclohexil sustituido opcionalmente con 1 o 2 R^{119}, o cicloheptil sustituido opcionalmente con 1 o 2 R^{119}.

[0068] En algunas formas de realización de compuestos de la Fórmula Ik, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ik, Cy_{12} es ciclopentil sustituido opcionalmente con 1 o 2 flúor, o 1o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; ciclohexil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; o cicloheptil sustituido opcionalmente con 1 o 2 flúor, o 1or 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior.

[0069] En algunas formas de realización de compuestos de la Fórmula Ik, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ik, Cy_{12} es ciclopentil, ciclopentil sustituido con 1 o 2 flúor, ciclopentil sustituido

con 1 o 2 alquil inferior, ciclopentil sustituido con 1 o 2 -OH, o ciclopentil sustituido con 1 o 2 alcoxi inferior.

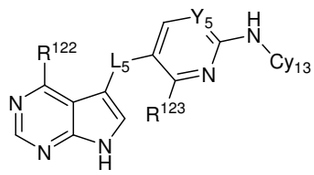
[0070] En algunas formas de realización de compuestos de la Fórmula Ik, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ik, Cy_{12} es ciclohexil, ciclohexil sustituido con 1 o 2 flúor, ciclohexil sustituido con 1 o 2 alquil inferior, ciclohexil sustituido con 1 o 2 -OH, o ciclohexil sustituido con 1 o 2 alcoxi inferior.

[0071] En algunas formas de realización de compuestos de la Fórmula Ik, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ik, Cy_{12} es cicloheptil, cicloheptil sustituido con 1 o 2 flúor, cicloheptil sustituido con 1 o 2 alquil inferior, cicloheptil sustituido con 1 o 2 -OH, o cicloheptil sustituido con 1 o 2 alcoxi inferior.

[0072] En algunas formas de realización de compuestos de la Fórmula Ik, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ik, L_4 es -C(H_2)-. En algunas formas de realización de compuestos de la Fórmula Ik, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ik, L_4 es -C(O)-.

[0073] En algunas formas de realización de compuestos de la Fórmula Ik, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ik, Y_4 es –N= y R^{118} es hidrógeno. En algunas formas de realización de compuestos de la Fórmula Ik, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ik, Y_4 es -C(H)= y R^{118} es flúor.

[0074] En un treceavo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Im:



Fórmula Im

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Y_5 es –N= y R^{123} es hidrógeno; o Y_5 es -C(H)= y R^{123} es flúor;

L_5 es -$C(H_2)$- o -C(O)-;

Cy_{13} es cicloalquil sustituido opcionalmente con una o más R^{124};

R^{122} se selecciona del grupo que consiste de cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{125}, y -O-R^{126};

Cada R^{124} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor y alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{125} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{126} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0075] En algunas formas de realización de compuestos de la Fórmula Im, R^{122} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización R^{122} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización R^{122} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi, y 2-metoxi-etoxi.

[0076] En algunas formas de realización de compuestos de la Fórmula Im, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Im, Cy_{13} es ciclopentil sustituido opcionalmente con 1 o 2 R^{124}, ciclohexil sustituido opcionalmente con 1 o 2 R^{124}, o cicloheptil sustituido opcionalmente con 1 o 2 R^{124}.

[0077] En algunas formas de realización de compuestos de la Fórmula Im, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Im, Cy_{13} es ciclopentil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; ciclohexil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; o cicloheptil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior.

[0078] En algunas formas de realización de compuestos de la Fórmula Im, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Im, Cy_{13} es ciclopentil, ciclopentil sustituido con 1 o 2 flúor, ciclopentil sustituido con 1 o 2 alquil inferior, ciclopentil sustituido con 1 o 2 -OH, o ciclopentil sustituido con 1 o 2 alcoxi inferior.

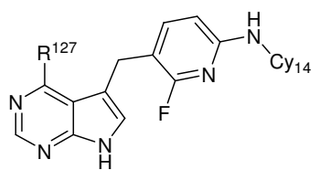
[0079] En algunas formas de realización de compuestos de la Fórmula Im, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Im, Cy_{13} es ciclohexil, ciclohexil sustituido con 1 o 2 flúor, ciclohexil sustituido con 1 o 2 alquil inferior, ciclohexil sustituido con 1 o 2 -OH, o ciclohexil sustituido con 1 o 2 alcoxi inferior.

[0080] En algunas formas de realización de compuestos de la Fórmula Im, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Im, Cy_{13} es cicloheptil, cicloheptil sustituido con 1 o 2 flúor, cicloheptil sustituido con 1 o 2 alquil inferior, cicloheptil sustituido con 1 o 2 -OH, o cicloheptil sustituido con 1 o 2 alcoxi inferior.

[0081] En algunas formas de realización de compuestos de la Fórmula Im, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Im, L_5 es -C(H_2)-. En algunas formas de realización de compuestos de la Fórmula Im, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Im, L_5 es -C(O)-.

[0082] En algunas formas de realización de compuestos de la Fórmula Im, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Im, Y_5 es –N= y R^{123} es hidrógeno. En algunas formas de realización de compuestos de la Fórmula Im, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Im, Y_5 es -C(H)= y R^{123} es flúor.

[0083] En un catorceavo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula In:



Fórmula In

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Cy_{14} es cicloalquil sustituido opcionalmente con una o más R^{128};

R^{127} se selecciona del grupo que consiste de cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{129} y -O-R^{130};

Cada R^{128} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{129} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{130} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0084] En algunas formas de realización de compuestos de la Fórmula In, R^{127} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización R^{127} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización R^{127} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi, y 2-metoxi-etoxi.

[0085] En algunas formas de realización de compuestos de la Fórmula In, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula In, Cy_{14} es ciclopentil sustituido opcionalmente con 1 o 2 R^{128}, ciclohexil sustituido opcionalmente con 1 o 2 R^{128}, o cicloheptil sustituido opcionalmente con 1 o 2 R^{128}.

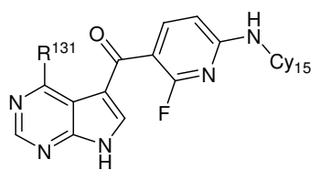
[0086] En algunas formas de realización de compuestos de la Fórmula In, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula In, Cy_{14} es ciclopentil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; ciclohexil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; o cicloheptil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior.

[0087] En algunas formas de realización de compuestos de la Fórmula In, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula In, Cy_{14} es ciclopentil, ciclopentil sustituido con 1 o 2 flúor, ciclopentil sustituido con 1 o 2 alquil inferior, ciclopentil sustituido con 1 o 2 -OH, o ciclopentil sustituido con 1 o 2 alcoxi inferior.

[0088] En algunas formas de realización de compuestos de la Fórmula In, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula In, Cy_{14} es ciclohexil, ciclohexil sustituido con 1 o 2 flúor, ciclohexil sustituido con 1 o 2 alquil inferior, ciclohexil sustituido con 1 o 2 -OH, o ciclohexil sustituido con 1 o 2 alcoxi inferior.

[0089] En algunas formas de realización de compuestos de la Fórmula In, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula In, Cy_{14} es cicloheptil, cicloheptil sustituido con 1 o 2 flúor, cicloheptil sustituido con 1 o 2 alquil inferior, cicloheptil sustituido con 1 o 2 -OH, o cicloheptil sustituido con 1 o 2 alcoxi inferior.

[0090] En un quinceavo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Io:



Fórmula Io

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Cy_{15} es cicloalquil sustituido opcionalmente con una o más R^{132};

R^{131} se selecciona del grupo que consiste de cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{133} y -O-R^{134};

Cada R^{132} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor y alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{133} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{134} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0091] En algunas formas de realización de compuestos de la Fórmula Io, R^{131} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización R^{131} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización R^{131} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi, y 2-metoxi-etoxi.

[0092] En algunas formas de realización de compuestos de la Fórmula Io, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Io, Cy_{15} es ciclopentil sustituido opcionalmente con 1 o 2 R^{132}, ciclohexil sustituido opcionalmente con 1 o 2 R^{132}, o cicloheptil sustituido opcionalmente con 1 o 2 R^{132}.

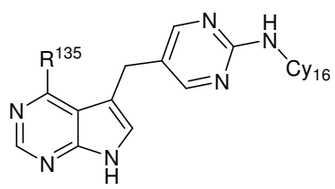
[0093] En algunas formas de realización de compuestos de la Fórmula Io, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Io, Cy_{15} es ciclopentil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; ciclohexil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; o cicloheptil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior.

[0094] En algunas formas de realización de compuestos de la Fórmula Io, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Io, Cy_{15} es ciclopentil, ciclopentil sustituido con 1 o 2 flúor, ciclopentil sustituido con 1 o 2 alquil inferior, ciclopentil sustituido con 1 o 2 -OH, o ciclopentil sustituido con 1 o 2 alcoxi inferior.

[0095] En algunas formas de realización de compuestos de la Fórmula Io, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Io, Cy_{15} es ciclohexil, ciclohexil sustituido con 1 o 2 flúor, ciclohexil sustituido con 1 o 2 alquil inferior, ciclohexil sustituido con 1 o 2 -OH, o ciclohexil sustituido con 1 o 2 alcoxi inferior.

[0096] En algunas formas de realización de compuestos de la Fórmula Io, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Io, Cy_{15} es cicloheptil, cicloheptil sustituido con 1 o 2 flúor, cicloheptil sustituido con 1 o 2 alquil inferior, cicloheptil sustituido con 1 o 2 -OH, o cicloheptil sustituido con 1 o 2 alcoxi inferior.

[0097] En dieciseisavo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ip:



Fórmula Ip

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo,donde:

Cy_{16} es cicloalquil sustituido opcionalmente con una o más R^{136};

R^{135} se selecciona del grupo que consiste de cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{137}, y -O-R^{138};

Cada R^{136} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{137} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{138} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0098] En algunas formas de realización de compuestos de la Fórmula Ip, R^{135} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización R^{135} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización R^{135} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi, y 2-metoxi-etoxi.

[0099] En algunas formas de realización de compuestos de la Fórmula Ip, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ip, Cy_{16} es ciclopentil sustituido opcionalmente con 1 o 2 R^{136}, ciclohexil sustituido opcionalmente con 1 o 2 R^{136}, o cicloheptil sustituido opcionalmente con 1 o 2 R^{136}.

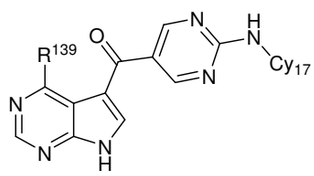
[0100] En algunas formas de realización de compuestos de la Fórmula Ip, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ip, Cy_{16} es ciclopentil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; ciclohexil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; o cicloheptil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior.

[0101] En algunas formas de realización de compuestos de la Fórmula Ip, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ip, Cy_{16} es ciclopentil, ciclopentil sustituido con 1 o 2 flúor, ciclopentil sustituido con 1 o 2 alquil inferior, ciclopentil sustituido con 1 o 2 -OH, o ciclopentil sustituido con 1 o 2 alcoxi inferior.

[0102] En algunas formas de realización de compuestos de la Fórmula Ip, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ip, Cy_{16} es ciclohexil, ciclohexil sustituido con 1 o 2 flúor, ciclohexil sustituido con 1 o 2 alquil inferior, ciclohexil sustituido con 1 o 2 -OH, o ciclohexil sustituido con 1 o 2 alcoxi inferior.

[0103] En algunas formas de realización de compuestos de la Fórmula Ip, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ip, Cy_{16} es cicloheptil, cicloheptil sustituido con 1 o 2 flúor, cicloheptil sustituido con 1 o 2 alquil inferior, cicloheptil sustituido con 1 o 2 -OH, o cicloheptil sustituido con 1 o 2 alcoxi inferior.

[0104] En un diecisieteavo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iq:



Fórmula Iq

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Cy_{16} es cicloalquil sustituido opcionalmente con una o más R^{140};

R^{139} se selecciona del grupo que consiste de cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{141} y -O-R^{142};

Cada R^{140} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{141} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{142} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0105] En algunas formas de realización de compuestos de la Fórmula Iq, R^{139} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización R^{139} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización R^{139} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

[0106] En algunas formas de realización de compuestos de la Fórmula Iq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iq, Cy_{17} es ciclopentil sustituido opcionalmente con 1 o 2 R^{140}, ciclohexil sustituido opcionalmente con 1 o 2 R^{140}, o cicloheptil sustituido opcionalmente con 1 o 2 R^{140}.

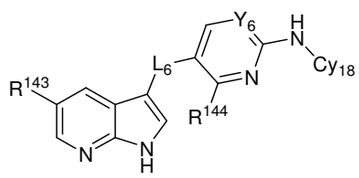
[0107] En algunas formas de realización de compuestos de la Fórmula Iq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iq, Cy_{17} es ciclopentil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; ciclohexil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; o cicloheptil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior.

[0108] En algunas formas de realización de compuestos de la Fórmula Iq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iq, Cy_{17} es ciclopentil, ciclopentil sustituido con 1 o 2 flúor, ciclopentil sustituido con 1 o 2 alquil inferior, ciclopentil sustituido con 1 o 2 -OH, o ciclopentil sustituido con 1 o 2 alcoxi inferior.

[0109] En algunas formas de realización de compuestos de la Fórmula Iq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iq, Cy_{17} es ciclohexil, ciclohexil sustituido con 1 o 2 flúor, ciclohexil sustituido con 1 o 2 alquil inferior, ciclohexil sustituido con 1 o 2 -OH, o ciclohexil sustituido con 1 o 2 alcoxi inferior.

[0110] En algunas formas de realización de compuestos de la Fórmula Iq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iq, Cy_{17} es cicloheptil, cicloheptil sustituido con 1 o 2 flúor, cicloheptil sustituido con 1 o 2 alquil inferior, cicloheptil sustituido con 1 o 2 -OH, o cicloheptil sustituido con 1 o 2 alcoxi inferior.

[0111] En un decimoctavo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ir:



Fórmula Ir

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Y_6 es –N= y R^{144} es hidrógeno; o Y_6 es -C(H)= y R^{144} es flúor;

L_6 es $-C(H_2)-$ o -C(O)-;

Cy_{18} es cicloalquil sustituido opcionalmente con una o más R^{145};

R^{143} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor; y

Cada R^{145} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor y alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0112] En algunas formas de realización de compuestos de la Fórmula Ir, R^{143} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{143} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{143} es hidrógeno, cloro o metil.

[0113] En algunas formas de realización de compuestos de la Fórmula Ir, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ir, Cy_{18} es ciclopentil sustituido opcionalmente con 1 o 2 R^{145}, ciclohexil sustituido opcionalmente con 1 o 2 R^{145}, o cicloheptil sustituido opcionalmente con 1 o 2 R^{145}.

[0114] En algunas formas de realización de compuestos de la Fórmula Ir, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ir, Cy_{18} es ciclopentil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; ciclohexil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; o cicloheptil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior.

[0115] En algunas formas de realización de compuestos de la Fórmula Ir, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ir, Cy_{18} es ciclopentil, ciclopentil sustituido con 1 o 2 flúor, ciclopentil sustituido con 1 o 2 alquil inferior, ciclopentil sustituido con 1 o 2 -OH, o ciclopentil sustituido con 1 o 2 alcoxi inferior.

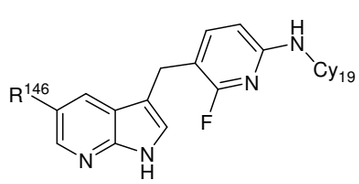
[0116] En algunas formas de realización de compuestos de la Fórmula Ir, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ir, Cy_{18} es ciclohexil, ciclohexil sustituido con 1 o 2 flúor, ciclohexil sustituido con 1 o 2 alquil inferior, ciclohexil sustituido con 1 o 2 -OH, o ciclohexil sustituido con 1 o 2 alcoxi inferior.

[0117] En algunas formas de realización de compuestos de la Fórmula Ir, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ir, Cy_{18} es cicloheptil, cicloheptil sustituido con 1 o 2 flúor, cicloheptil sustituido con 1 o 2 alquil inferior, cicloheptil sustituido con 1 o 2 -OH, o cicloheptil sustituido con 1 o 2 alcoxi inferior.

[0118] En algunas formas de realización de compuestos de la Fórmula Ir, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ir, L_6 es -$C(H_2)$-. En algunas formas de realización de compuestos de la Fórmula Ir, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ir, L_6 es -C(O)-.

[0119] En algunas formas de realización de compuestos de la Fórmula Ir, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ir, Y_6 es –N= y R^{144} es hidrógeno. En algunas formas de realización de compuestos de la Fórmula Ir, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ir, Y_6 es -C(H)= y R^{144} es flúor.

[0120] En un decimonoveno aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Is:



Fórmula Is

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Cy_{19} es cicloalquil sustituido opcionalmente con una o más R^{147};

R^{146} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor; y

Cada R^{147} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0121] En algunas formas de realización de compuestos de la Fórmula Is, R^{146} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{146} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{146} es hidrógeno, cloro o metil.

[0122] En algunas formas de realización de compuestos de la Fórmula Is, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Is, Cy_{19} es ciclopentil sustituido opcionalmente con 1 o 2 R^{147}, ciclohexil sustituido opcionalmente con 1 o 2 R^{147}, o cicloheptil sustituido opcionalmente con 1 o 2 R^{147}.

[0123] En algunas formas de realización de compuestos de la Fórmula Is, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Is, Cy_{19} es ciclopentil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; ciclohexil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; o cicloheptil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior.

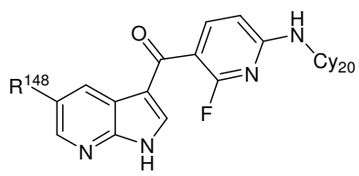
[0124] En algunas formas de realización de compuestos de la Fórmula Is, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Is, Cy_{19} es ciclopentil, ciclopentil sustituido con 1 o 2 flúor, ciclopentil sustituido con 1 o 2 alquil inferior, ciclopentil sustituido con 1 o 2 -OH, o ciclopentil sustituido con 1 o 2 alcoxi inferior.

[0125] En algunas formas de realización de compuestos de la Fórmula Is, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Is, Cy_{19} es ciclohexil, ciclohexil sustituido con 1 o 2 flúor, ciclohexil sustituido con 1 o 2 alquil inferior, ciclohexil sustituido con 1 o 2 -OH, o ciclohexil sustituido con 1 o 2 alcoxi inferior.

[0126] En algunas formas de realización de compuestos de la Fórmula Is, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Is, Cy_{19} es cicloheptil, cicloheptil sustituido con 1 o 2 flúor, cicloheptil sustituido con 1 o 2 alquil inferior, cicloheptil sustituido con 1 o 2 -OH, o cicloheptil sustituido con 1 o 2 alcoxi inferior.

[0127] En un vigésimo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula It:



Fórmula It

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo,donde:

Cy_{20} es cicloalquil sustituido opcionalmente con una o más R^{149};

R^{148} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor; y

Cada R^{149} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0128] En algunas formas de realización de compuestos de la Fórmula It, R^{148} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{148} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{148} es hidrógeno, cloro o metil.

[0129] En algunas formas de realización de compuestos de la Fórmula It, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula It, Cy_{20} es ciclopentil sustituido opcionalmente con 1 o 2 R^{149}, ciclohexil sustituido opcionalmente con 1 o 2 R^{149}, o cicloheptil sustituido opcionalmente con 1 o 2 R^{149}.

[0130] En algunas formas de realización de compuestos de la Fórmula It, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula It, Cy_{20} es ciclopentil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; ciclohexil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; o cicloheptil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior.

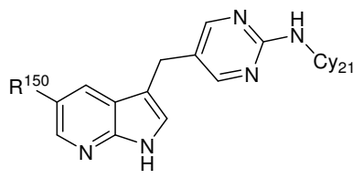
[0131] En algunas formas de realización de compuestos de la Fórmula It, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula It, Cy_{20} es ciclopentil, ciclopentil sustituido con 1 o 2 flúor, ciclopentil sustituido con 1 o 2 alquil inferior, ciclopentil sustituido con 1 o 2 -OH, o ciclopentil sustituido con 1 o 2 alcoxi inferior.

[0132] En algunas formas de realización de compuestos de la Fórmula It, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula It, Cy_{20} es ciclohexil, ciclohexil sustituido con 1 o 2 flúor, ciclohexil sustituido con 1 o 2 alquil inferior, ciclohexil sustituido con 1 o 2 -OH, o ciclohexil sustituido con 1 o 2 alcoxi inferior.

[0133] En algunas formas de realización de compuestos de la Fórmula It, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula It, Cy_{20} es cicloheptil, cicloheptil sustituido con 1 o 2 flúor, cicloheptil sustituido con 1 o 2

alquil inferior, cicloheptil sustituido con 1 o 2 -OH, o cicloheptil sustituido con 1 o 2 alcoxi inferior.

[0134] En un vigésimo-primer aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iu:



Fórmula Iu

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Cy_{21} es cicloalquil sustituido opcionalmente con una o más R^{151};

R^{150} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor; y

Cada R^{151} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor, y alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0135] En algunas formas de realización de compuestos de la Fórmula Iu, R^{150} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{150} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{150} es hidrógeno, cloro o metil.

[0136] En algunas formas de realización de compuestos de la Fórmula Iu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iu, Cy_{21} es ciclopentil sustituido opcionalmente con 1 o 2 R^{151}, ciclohexil sustituido opcionalmente con 1 o 2 R^{151}, o cicloheptil sustituido opcionalmente con 1 o 2 R^{151}.

[0137] En algunas formas de realización de compuestos de la Fórmula Iu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

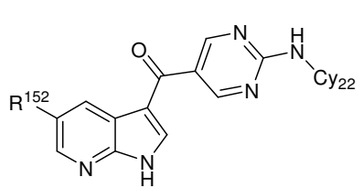
Iu, Cy_{21} es ciclopentil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; ciclohexil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; o cicloheptil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior.

[0138] En algunas formas de realización de compuestos de la Fórmula Iu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iu, Cy_{21} es ciclopentil, ciclopentil sustituido con 1 o 2 flúor, ciclopentil sustituido con 1 o 2 alquil inferior, ciclopentil sustituido con 1 o 2 -OH, o ciclopentil sustituido con 1 o 2 alcoxi inferior.

[0139] En algunas formas de realización de compuestos de la Fórmula Iu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iu, Cy_{21} es ciclohexil, ciclohexil sustituido con 1 o 2 flúor, ciclohexil sustituido con 1 o 2 alquil inferior, ciclohexil sustituido con 1 o 2 -OH, o ciclohexil sustituido con 1 o 2 alcoxi inferior.

[0140] En algunas formas de realización de compuestos de la Fórmula Iu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iu, Cy_{21} es cicloheptil, cicloheptil sustituido con 1 o 2 flúor, cicloheptil sustituido con 1 o 2 alquil inferior, cicloheptil sustituido con 1 o 2 -OH, o cicloheptil sustituido con 1 o 2 alcoxi inferior.

[0141] En un vigésimo-segundo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iv:



Fórmula Iv

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Cy_{22} es cicloalquil sustituido opcionalmente con una o más R^{153};

R^{152} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor; y

Cada R^{153} se selecciona independientemente del grupo que consiste de flúor, -OH, alquil inferior sustituido opcionalmente con uno o más flúor y alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0142] En algunas formas de realización de compuestos de la Fórmula Iv, R^{152} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{152} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{152} es hidrógeno, cloro o metil.

[0143] En algunas formas de realización de compuestos de la Fórmula Iv, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iv, Cy_{22} es ciclopentil sustituido opcionalmente con 1 o 2 R^{153}, ciclohexil sustituido opcionalmente con 1 o 2 R^{153}, o cicloheptil sustituido opcionalmente con 1 o 2 R^{153}.

[0144] En algunas formas de realización de compuestos de la Fórmula Iv, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iv, Cy_{22} es ciclopentil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; ciclohexil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior; o cicloheptil sustituido opcionalmente con 1 o 2 flúor, o 1 o 2 alquil inferior, o 1 o 2 -OH, o 1 o 2 alcoxi inferior.

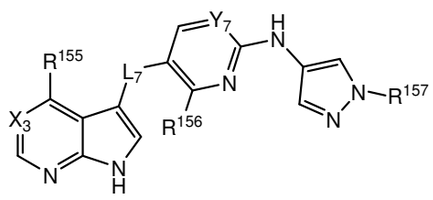
[0145] En algunas formas de realización de compuestos de la Fórmula Iv, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Iv, Cy_{22} es ciclopentil, ciclopentil sustituido con 1 o 2 flúor, ciclopentil sustituido con 1 o 2 alquil inferior, ciclopentil sustituido con 1 o 2 -OH, o ciclopentil sustituido con 1 o 2 alcoxi inferior.

[0146] En algunas formas de realización de compuestos de la Fórmula Iv, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iv, Cy_{22} es ciclohexil, ciclohexil sustituido con 1 o 2 flúor, ciclohexil sustituido con 1 o 2 alquil inferior, ciclohexil sustituido con 1 o 2 -OH, o ciclohexil sustituido con 1 o 2 alcoxi inferior.

[0147] En algunas formas de realización de compuestos de la Fórmula Iv, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iv, Cy_{22} es cicloheptil, cicloheptil sustituido con 1 o 2 flúor, cicloheptil sustituido con 1 o 2 alquil inferior, cicloheptil sustituido con 1 o 2 -OH, o cicloheptil sustituido con 1 o 2 alcoxi inferior.

[0148] En un vigésimo-tercer aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iw:



Fórmula Iw

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

X_3 es –N=, -C(H)=, o -C(R^{154})= ;

Y_7 es –N= y R^{156} es hidrógeno; o Y_7 es -C(H)= y R^{156} es flúor;

L_7 es -C(H_2)- o -C(O)-;

Donde X_3 es -C(R^{154})=, R^{155} es hidrógeno;

Donde X_3 es –N= o -C(H)=, R^{155} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{158} y -O-R^{159};

R^{154} es flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{157} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{158} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{159} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0149] En algunas formas de realización de compuestos de la Fórmula Iw, X_3 es –N= y R^{155} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{158} y -O-R^{159}. En una de las formas de realización, X_3 es –N= y R^{155} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, X_3 es –N= y R^{155} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, X_3 es -N= y R^{155} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi, y 2-metoxi-etoxi.

[0150] En algunas formas de realización de compuestos de la Fórmula Iw, X_3 es -C(H)= o -C(R^{154})= y R^{154} es flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor. En una de las formas de realización, X_3 es -C(H)= o -C(R^{154})= y R^{154} es cloro o alquil inferior. En una de las formas de realización, X_3 es -C(H)= o -C(R^{154})= y R^{154} es cloro o C_{1-3} alquil. En una de las formas de realización, X_3 es -C(H)= o -C(R^{154})= y R^{154} es cloro o metil.

[0151] En algunas formas de realización de compuestos de la Fórmula Iw, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iw, R^{157} es cicloalquil o alquil inferior.

[0152] En algunas formas de realización de compuestos de la Fórmula Iw, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iw, R^{157} es C_{3-6} cicloalquil o alquil inferior.

[0153] En algunas formas de realización de compuestos de la Fórmula Iw, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iw, R^{157} es ciclopropil o alquil inferior.

[0154] En algunas formas de realización de compuestos de la Fórmula Iw, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iw, R^{157} es alquil inferior.

[0155] En algunas formas de realización de compuestos de la Fórmula Iw, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iw, R^{157} es C_{1-3} alquil.

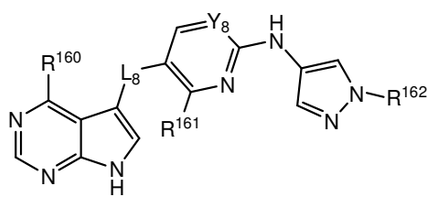
[0156] En algunas formas de realización de compuestos de la Fórmula Iw, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iw, R^{157} es etil.

[0157] En algunas formas de realización de compuestos de la Fórmula Iw, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iw, L_7 es $-C(H_2)-$. En algunas formas de realización de compuestos de la Fórmula Iw, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iw, L_7 es $-C(O)-$.

[0158] En algunas formas de realización de compuestos de la Fórmula Iw, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Iw, Y_7 es –N= y R^{156} es hidrógeno. En algunas formas de realización de compuestos de la Fórmula Iw, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iw, Y_7 es -C(H)= y R^{156} es flúor.

[0159] En un vigésimo-cuarto aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ix:



Fórmula Ix

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Y_8 es –N= y R^{161} es hidrógeno; o Y_8 es -C(H)= y R^{161} es flúor;

L_8 es -$C(H_2)$- o -C(O)-;

R^{160} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{163}, y -O-R^{164};

R^{162} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{163} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{164} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0160] En algunas formas de realización de compuestos de la Fórmula Ix, R^{160} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{160} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{160} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi, y 2-metoxi-etoxi.

[0161] En algunas formas de realización de compuestos de la Fórmula Ix, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ix, R^{162} es cicloalquil o alquil inferior.

[0162] En algunas formas de realización de compuestos de la Fórmula Ix, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ix, R^{162} es C_{3-6} cicloalquil o alquil inferior.

[0163] En algunas formas de realización de compuestos de la Fórmula Ix, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ix, R^{162} es ciclopropil o alquil inferior.

[0164] En algunas formas de realización de compuestos de la Fórmula Ix, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ix, R^{162} es alquil inferior.

[0165] En algunas formas de realización de compuestos de la Fórmula Ix, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ix, R^{162} es C_{1-3} alquil.

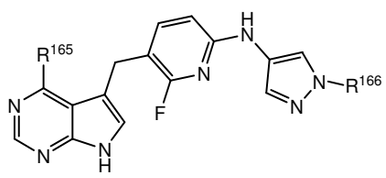
[0166] En algunas formas de realización de compuestos de la Fórmula Ix, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ix, R^{162} es etil.

[0167] En algunas formas de realización de compuestos de la Fórmula Ix, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ix, L_8 es $-C(H_2)-$. En algunas formas de realización de compuestos de la Fórmula Ix, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ix, L_8 es -C(O)-.

[0168] En algunas formas de realización de compuestos de la Fórmula Ix, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Ix, Y_8 es –N= y R^{161} es hidrógeno. En algunas formas de realización de compuestos de la Fórmula Ix, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ix, Y_8 es -C(H)= y R^{161} es flúor.

[0169] En un vigésimo-quinto aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iy:



Fórmula Iy

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{165} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{167}, y -O-R^{168};

R^{166} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{167} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{168} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0170] En algunas formas de realización de compuestos de la Fórmula Iy, R^{165} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{165} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{165} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi, y 2-metoxi-etoxi.

[0171] En algunas formas de realización de compuestos de la Fórmula Iy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iy, R^{166} es cicloalquil o alquil inferior.

[0172] En algunas formas de realización de compuestos de la Fórmula Iy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iy, R^{166} es C_{3-6} cicloalquil o alquil inferior.

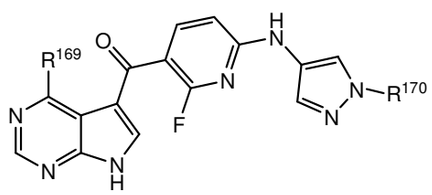
[0173] En algunas formas de realización de compuestos de la Fórmula Iy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iy, R^{166} es ciclopropil o alquil inferior.

[0174] En algunas formas de realización de compuestos de la Fórmula Iy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iy, R^{166} es alquil inferior.

[0175] En algunas formas de realización de compuestos de la Fórmula Iy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iy, R^{166} es C_{1-3} alquil.

[0176] En algunas formas de realización de compuestos de la Fórmula Iy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iy, R^{166} es etil.

[0177] En un vigésimo-sexto aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iz:



Fórmula Iz

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{169} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{171} y -O-R^{172};

R^{170} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{171} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{172} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0178] En algunas formas de realización de compuestos de la Fórmula Iz, R^{169} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{169} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{169} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

[0179] En algunas formas de realización de compuestos de la Fórmula Iz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iz, R^{170} es cicloalquil o alquil inferior.

[0180] En algunas formas de realización de compuestos de la Fórmula Iz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iz, R^{170} es C_{3-6} cicloalquil o alquil inferior.

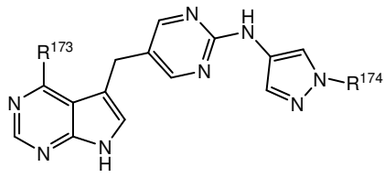
[0181] En algunas formas de realización de compuestos de la Fórmula Iz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iz, R^{170} es ciclopropil o alquil inferior.

[0182] En algunas formas de realización de compuestos de la Fórmula Iz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iz, R^{170} es alquil inferior.

[0183] En algunas formas de realización de compuestos de la Fórmula Iz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iz, R^{170} es C_{1-3} alquil.

[0184] En algunas formas de realización de compuestos de la Fórmula Iz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iz, R^{170} es etil.

[0185] En un vigésimo-séptimo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iaa:



Fórmula Iaa

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{173} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{175} y -O-R^{176};

R^{174} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{175} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{176} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0186] En algunas formas de realización de compuestos de la Fórmula Iaa, R^{173} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{173} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{173} se

selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

[0187] En algunas formas de realización de compuestos de la Fórmula Iaa, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iaa, R^{174} es cicloalquil o alquil inferior.

[0188] En algunas formas de realización de compuestos de la Fórmula Iaa, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iaa, R^{174} es C_{3-6} cicloalquil o alquil inferior.

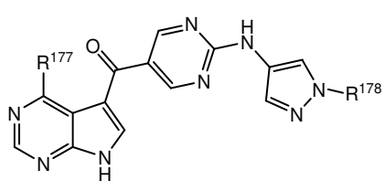
[0189] En algunas formas de realización de compuestos de la Fórmula Iaa, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iaa, R^{174} es ciclopropil o alquil inferior.

[0190] En algunas formas de realización de compuestos de la Fórmula Iaa, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iaa, R^{174} es alquil inferior.

[0191] En algunas formas de realización de compuestos de la Fórmula Iaa, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iaa, R^{174} es C_{1-3} alquil.

[0192] En algunas formas de realización de compuestos de la Fórmula Iaa, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iaa, R^{174} es etil.

[0193] En un vigésimo-octavo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ibb:



Fórmula Ibb

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{177} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{179} y -O-R^{180};

R^{178} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{179} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{180} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0194] En algunas formas de realización de compuestos de la Fórmula Ibb, R^{177} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{177} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{177} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

[0195] En algunas formas de realización de compuestos de la Fórmula Ibb, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ibb, R^{178} es cicloalquil o alquil inferior.

[0196] En algunas formas de realización de compuestos de la Fórmula Ibb, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ibb, R^{178} es C_{3-6} cicloalquil o alquil inferior.

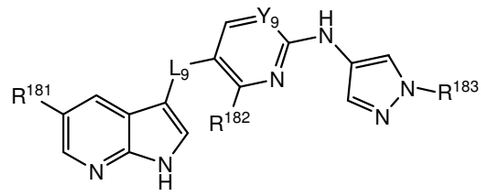
[0197] En algunas formas de realización de compuestos de la Fórmula Ibb, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ibb, R^{178} es ciclopropil o alquil inferior.

[0198] En algunas formas de realización de compuestos de la Fórmula Ibb, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ibb, R^{178} es alquil inferior.

[0199] En algunas formas de realización de compuestos de la Fórmula Ibb, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ibb, R^{178} es C_{1-3} alquil.

[0200] En algunas formas de realización de compuestos de la Fórmula Ibb, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ibb, R^{178} es etil.

[0201] En un vigésimo-noveno aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Icc:



Fórmula Icc

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Y_9 es –N= y R^{182} es hidrógeno; o Y_9 es -C(H)= y R^{182} es flúor;

L_9 es $-C(H_2)-$ o -C(O)-;

R^{181} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{183} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor.

[0202] En algunas formas de realización de compuestos de la Fórmula Icc, R^{181} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{181} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{181} es hidrógeno, cloro o metil.

[0203] En algunas formas de realización de compuestos de la Fórmula Icc, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Icc, R^{183} es cicloalquil o alquil inferior.

[0204] En algunas formas de realización de compuestos de la Fórmula Icc, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Icc, R^{183} es C_{3-6} cicloalquil o alquil inferior.

[0205] En algunas formas de realización de compuestos de la Fórmula Icc, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Icc, R^{183} es ciclopropil o alquil inferior.

[0206] En algunas formas de realización de compuestos de la Fórmula Icc, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Icc, R^{183} es alquil inferior.

[0207] En algunas formas de realización de compuestos de la Fórmula Icc, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Icc, R^{183} es C_{1-3} alquil.

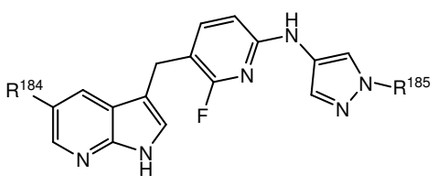
[0208] En algunas formas de realización de compuestos de la Fórmula Icc, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Icc, R^{183} es etil.

[0209] En algunas formas de realización de compuestos de la Fórmula Icc, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Icc, L_9 es $-C(H_2)-$. En algunas formas de realización de compuestos de la Fórmula Icc, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Icc, L_9 es -C(O)-.

[0210] En algunas formas de realización de compuestos de la Fórmula Icc, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Icc, Y_9 es –N= y R^{182} es hidrógeno. En algunas formas de realización de compuestos de la Fórmula Icc, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Icc, Y_9 es -C(H)= y R^{182} es flúor.

[0211] En un trigésimo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Idd:



Fórmula Idd

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{184} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{185} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor.

[0212] En algunas formas de realización de compuestos de la Fórmula Idd, R^{184} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{184} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{184} es hidrógeno, cloro o metil.

[0213] En algunas formas de realización de compuestos de la Fórmula Idd, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Idd, R^{185} es cicloalquil o alquil inferior.

[0214] En algunas formas de realización de compuestos de la Fórmula Idd, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Idd, R^{185} es C_{3-6} cicloalquil o alquil inferior.

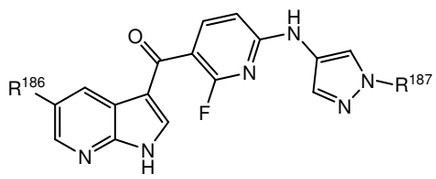
[0215] En algunas formas de realización de compuestos de la Fórmula Idd, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Idd, R^{185} es ciclopropil o alquil inferior.

[0216] En algunas formas de realización de compuestos de la Fórmula Idd, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Idd, R^{185} es alquil inferior.

[0217] En algunas formas de realización de compuestos de la Fórmula Idd, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Idd, R^{185} es C_{1-3} alquil.

[0218] En algunas formas de realización de compuestos de la Fórmula Idd, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Idd, R^{185} es etil.

[0219] En un trigésimo-primer aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iee:



Fórmula Iee

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{186} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{187} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor.

[0220] En algunas formas de realización de compuestos de la Fórmula Iee, R^{186} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{186} es

hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{186} es hidrógeno, cloro o metil.

[0221] En algunas formas de realización de compuestos de la Fórmula Iee, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iee, R^{187} es cicloalquil o alquil inferior.

[0222] En algunas formas de realización de compuestos de la Fórmula Iee, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iee, R^{187} es C_{3-6} cicloalquil o alquil inferior.

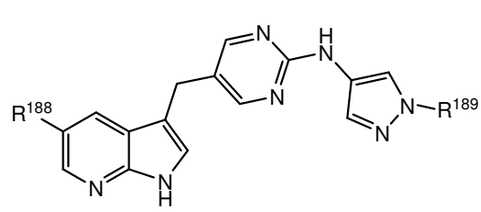
[0223] En algunas formas de realización de compuestos de la Fórmula Iee, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iee, R^{187} es ciclopropil o alquil inferior.

[0224] En algunas formas de realización de compuestos de la Fórmula Iee, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iee, R^{187} es alquil inferior.

[0225] En algunas formas de realización de compuestos de la Fórmula Iee, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iee, R^{187} es C_{1-3} alquil.

[0226] En algunas formas de realización de compuestos de la Fórmula Iee, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iee, R^{187} es etil.

[0227] En un trigésimo-segundo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iff:



Fórmula Iff

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{188} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{189} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor.

[0228] En algunas formas de realización de compuestos de la Fórmula Iff, R^{188} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{188} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{188} es hidrógeno, cloro o metil.

[0229] En algunas formas de realización de compuestos de la Fórmula Iff, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iff, R^{189} es cicloalquil o alquil inferior.

[0230] En algunas formas de realización de compuestos de la Fórmula Iff, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iff, R^{189} es C_{3-6} cicloalquil o alquil inferior.

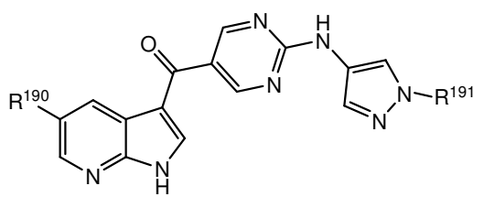
[0231] En algunas formas de realización de compuestos de la Fórmula Iff, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iff, R^{189} es ciclopropil o alquil inferior.

[0232] En algunas formas de realización de compuestos de la Fórmula Iff, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iff, R^{189} es alquil inferior.

[0233] En algunas formas de realización de compuestos de la Fórmula Iff, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iff, R^{189} es C_{1-3} alquil.

[0234] En algunas formas de realización de compuestos de la Fórmula Iff, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iff, R^{189} es etil.

[0235] En un trigésimo-tercero aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Igg:



Fórmula Igg

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{190} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{191} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor.

[0236] En algunas formas de realización de compuestos de la Fórmula Igg, R^{190} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{190} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{190} es hidrógeno, cloro o metil.

[0237] En algunas formas de realización de compuestos de la Fórmula Igg, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Igg, R^{191} es cicloalquil o alquil inferior.

[0238] En algunas formas de realización de compuestos de la Fórmula Igg, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Igg, R^{191} es C_{3-6} cicloalquil o alquil inferior.

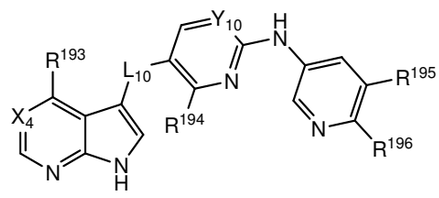
[0239] En algunas formas de realización de compuestos de la Fórmula Igg, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Igg, R^{191} es ciclopropil o alquil inferior.

[0240] En algunas formas de realización de compuestos de la Fórmula Igg, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Igg, R^{191} es alquil inferior.

[0241] En algunas formas de realización de compuestos de la Fórmula Igg, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Igg, R^{191} es C_{1-3} alquil.

[0242] En algunas formas de realización de compuestos de la Fórmula Igg, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Igg, R^{191} es etil.

[0243] En un trigésimo-cuarto aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ihh:



Fórmula Ihh

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

X_4 es –N=, -C(H)=, o -C(R^{192})= ;

Y_{10} es –N= y R^{194} es hidrógeno; o Y_{10} es -C(H)= y R^{194} es flúor;

L_{10} es -C(H_2)- o -C(O)-;

Donde X_4 es -C(R^{192})=, R^{193} es hidrógeno;

Donde X_4 es –N= o -C(H)=, R^{193} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{197}, y -O-R^{198};

R^{192} es flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{195} es hidrógeno y R^{196} es hidrógeno, flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{196} es hidrógeno y R^{195} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{197} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{198} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0244] En algunas formas de realización de compuestos de la Fórmula Ihh, X_4 es –N= y R^{193} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{197} y -O-R^{198}. En una de las formas de realización, X_4 es –N= y R^{193} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, X_4 es –N= y R^{193} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, X_4 es -N= y R^{193} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

[0245] En algunas formas de realización de compuestos de la Fórmula Ihh, X_4 es -C(H)= o -C(R^{192})= y R^{192} es flúor, cloro, o alquil inferior sustituido opcionalmente

con uno o más flúor. En una de las formas de realización, X_4 es -C(H)= o -C(R^{192})= y R^{192} es cloro o alquil inferior. En una de las formas de realización, X_4 es -C(H)= o -C(R^{192})= y R^{192} es cloro o C_{1-3} alquil. En una de las formas de realización, X_4 es -C(H)= o -C(R^{192})= y R^{192} es cloro o metil.

[0246] En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{196} es hidrógeno y R^{195} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{196} es hidrógeno y R^{195} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{196} es hidrógeno y R^{195} es alquil inferior. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{196} es hidrógeno y R^{195} es C_{1-3} alquil. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{196} es hidrógeno y R^{195} es metil.

[0247] En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización

antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es flúor, cloro, bromo. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0248] En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es cicloalquil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es ciclopropil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es ciclopropil, trifluorometil, metil o etil.

[0249] En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es cicloalquil. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es ciclopropil.

[0250] En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Ihh, R^{195} es hidrógeno y R^{196} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es trifluorometil, metil o etil. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es trifluorometil. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es metil. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es etil.

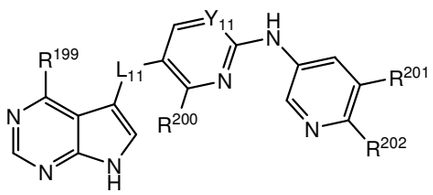
[0251] En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es C_{1-3} alcoxi. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es metoxi o etoxi. En algunas formas de realización de compuestos

de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es metoxi. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, R^{195} es hidrógeno y R^{196} es etoxi.

[0252] En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, L_{10} es $-C(H_2)-$. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, L_{10} es -C(O)-.

[0253] En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, Y_{10} es –N= y R^{194} es hidrógeno. En algunas formas de realización de compuestos de la Fórmula Ihh, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ihh, Y_{10} es -C(H)= y R^{194} es flúor.

[0254] En un trigésimo-quinto aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iii:



Fórmula Iii

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Y_{11} es –N= y R^{200} es hidrógeno; o Y_{11} es -C(H)= y R^{200} es flúor;

L_{11} es $-C(H_2)-$ o -C(O)-;

R^{199} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{203}, y -O-R^{204};

R^{201} es hidrógeno y R^{202} es hidrógeno, flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{202} es hidrógeno y R^{201} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{203} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{204} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0255] En algunas formas de realización de compuestos de la Fórmula Iii, R^{199} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{199} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{199} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

[0256] En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{202} es hidrógeno y R^{201} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{202} es hidrógeno y R^{201} es alquil inferior

sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{202} es hidrógeno y R^{201} es alquil inferior. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{202} es hidrógeno y R^{201} es C_{1-3} alquil. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{202} es hidrógeno y R^{201} es metil.

[0257] En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es flúor, cloro, bromo. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0258] En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es cicloalquil o C_{1-3} alquil sustituido

opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es ciclopropil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es ciclopropil, trifluorometil, metil o etil.

[0259] En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es cicloalquil. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es ciclopropil.

[0260] En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es trifluorometil, metil o etil. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es trifluorometil. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es

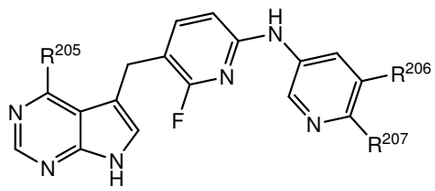
hidrógeno y R^{202} es metil. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es etil.

[0261] En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es C_{1-3} alcoxi. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es metoxi o etoxi. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es metoxi. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, R^{201} es hidrógeno y R^{202} es etoxi.

[0262] En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, L_{11} es $-C(H_2)-$. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, L_{11} es -C(O)-.

[0263] En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, Y_{11} es –N= y R^{200} es hidrógeno. En algunas formas de realización de compuestos de la Fórmula Iii, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iii, Y_{11} es -C(H)= y R^{200} es flúor.

[0264] En un trigésimo-sexto aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ijj:



Fórmula Ijj

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{205} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{208} y -O-R^{209};

R^{206} es hidrógeno y R^{207} es hidrógeno, flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{207} es hidrógeno y R^{206} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{208} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{209} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0265] En algunas formas de realización de compuestos de la Fórmula Ijj, R^{205} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y

alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{205} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{205} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

[0266] En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{207} es hidrógeno y R^{206} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{207} es hidrógeno y R^{206} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{207} es hidrógeno y R^{206} es alquil inferior. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{207} es hidrógeno y R^{206} es C_{1-3} alquil. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{207} es hidrógeno y R^{206} es metil.

[0267] En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de

compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es flúor, cloro, bromo. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0268] En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es cicloalquil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es ciclopropil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es ciclopropil, trifluorometil, metil o etil.

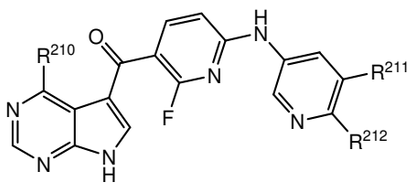
[0269] En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es cicloalquil. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es ciclopropil.

[0270] En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es trifluorometil, metil o etil. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es trifluorometil. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es metil. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es etil.

[0271] En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es C_{1-3} alcoxi. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a

cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es metoxi o etoxi. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es metoxi. En algunas formas de realización de compuestos de la Fórmula Ijj, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ijj, R^{206} es hidrógeno y R^{207} es etoxi.

[0272] En un trigésimo-séptimo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ikk:



Fórmula Ikk

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{210} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{213} y -O-R^{214};

R^{211} es hidrógeno y R^{212} es hidrógeno, flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{212} es hidrógeno y R^{211} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{213} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{214} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0273] En algunas formas de realización de compuestos de la Fórmula Ikk, R^{210} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{210} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{210} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

[0274] En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{212} es hidrógeno y R^{211} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{212} es hidrógeno y R^{211} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{212} es hidrógeno y R^{211} es alquil inferior. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{212} es hidrógeno y R^{211} es C_{1-3} alquil. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{212} es hidrógeno y R^{211} es metil.

[0275] En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es flúor, cloro, bromo, cicloalquil, alquil inferior

sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es flúor, cloro, bromo. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0276] En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es cicloalquil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es ciclopropil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es ciclopropil, trifluorometil, metil o etil.

[0277] En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es cicloalquil. En algunas formas de realización de

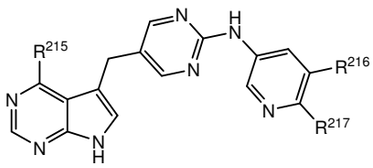
compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es ciclopropil.

[0278] En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es trifluorometil, metil o etil. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es trifluorometil. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es metil. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es etil.

[0279] En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización

antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es C_{1-3} alcoxi. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es metoxi o etoxi. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es metoxi. En algunas formas de realización de compuestos de la Fórmula Ikk, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ikk, R^{211} es hidrógeno y R^{212} es etoxi.

[0280] En un trigésimo-octavo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Imm:



Fórmula Imm

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{215} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{218} y -O-R^{219};

R^{216} es hidrógeno y R^{217} es hidrógeno, flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{217} es hidrógeno y R^{216} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{218} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{219} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0281] En algunas formas de realización de compuestos de la Fórmula Imm, R^{215} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{215} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{215} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

[0282] En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{217} es hidrógeno y R^{216} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{217} es hidrógeno y R^{216} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{217} es hidrógeno y R^{216} es alquil inferior. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{217} es hidrógeno y R^{216} es C_{1-3} alquil. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{217} es hidrógeno y R^{216} es metil.

[0283] En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es flúor, cloro, bromo. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0284] En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es cicloalquil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es ciclopropil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es ciclopropil, trifluorometil, metil o etil.

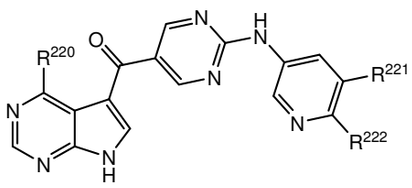
[0285] En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es cicloalquil. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es ciclopropil.

[0286] En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es trifluorometil, metil o etil. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es trifluorometil. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es metil. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es etil.

[0287] En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Imm,

adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es C_{1-3} alcoxi. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es metoxi o etoxi. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es metoxi. En algunas formas de realización de compuestos de la Fórmula Imm, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Imm, R^{216} es hidrógeno y R^{217} es etoxi.

[0288] En un trigésimo-noveno aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Inn:



Fórmula Inn

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{220} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{223} y -O-R^{224};

R^{221} es hidrógeno y R^{222} es hidrógeno, flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{222} es hidrógeno y R^{221} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{223} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor; y

R^{224} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior.

[0289] En algunas formas de realización de compuestos de la Fórmula Inn, R^{220} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{220} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{220} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi, y 2-metoxi-etoxi.

[0290] En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{222} es hidrógeno y R^{221} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{222} es hidrógeno y R^{221} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{222} es hidrógeno y R^{221} es alquil inferior. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{222} es

hidrógeno y R^{221} es C_{1-3} alquil. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{222} es hidrógeno y R^{221} es metil.

[0291] En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es flúor, cloro, bromo. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0292] En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es cicloalquil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es ciclopropil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización

antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es ciclopropil, trifluorometil, metil o etil.

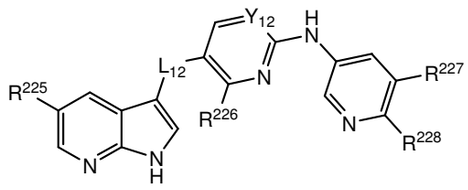
[0293] En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es cicloalquil. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es ciclopropil.

[0294] En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es trifluorometil, metil o etil. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es trifluorometil. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es metil. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es etil.

[0295] En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Inn, R^{221} es hidrógeno y R^{222} es alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es C_{1-3} alcoxi. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es metoxi o etoxi. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es metoxi. En algunas formas de realización de compuestos de la Fórmula Inn, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Inn, R^{221} es hidrógeno y R^{222} es etoxi.

[0296] En un cuadragésimo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ioo:



Fórmula Ioo

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Y_{12} es –N= y R^{226} es hidrógeno; o Y_{12} es -C(H)= y R^{226} es flúor;

L_{12} es $-C(H_2)-$ o -C(O)-;

R^{225} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{227} es hidrógeno y R^{228} es hidrógeno, flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{228} es hidrógeno y R^{227} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0297] En algunas formas de realización de compuestos de la Fórmula Ioo, R^{225} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{225} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{225} es hidrógeno, cloro o metil.

[0298] En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{228} es hidrógeno y R^{227} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{228} es hidrógeno y R^{227} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{228} es hidrógeno y R^{227} es alquil inferior. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{228} es hidrógeno y R^{227} es C_{1-3} alquil. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{228} es hidrógeno y R^{227} es metil.

[0299] En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es flúor, cloro, bromo. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0300] En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es cicloalquil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es ciclopropil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es ciclopropil, trifluorometil, metil o etil.

[0301] En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es cicloalquil. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es ciclopropil.

[0302] En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es trifluorometil, metil o etil. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es trifluorometil. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es metil. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es etil.

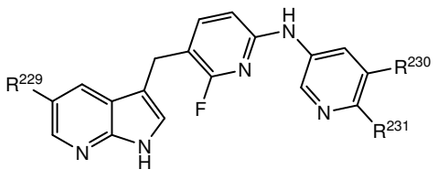
[0303] En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ioo,

adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es C_{1-3} alcoxi. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es metoxi o etoxi. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es metoxi. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, R^{227} es hidrógeno y R^{228} es etoxi.

[0304] En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, L_{12} es $-C(H_2)-$. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, L_{12} es -C(O)-.

[0305] En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, Y_{12} es –N= y R^{226} es hidrógeno. En algunas formas de realización de compuestos de la Fórmula Ioo, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ioo, Y_{12} es -C(H)= y R^{226} es flúor.

[0306] En un cuadragésimo-primero aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ipp:



Fórmula Ipp

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{229} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{230} es hidrógeno y R^{231} es hidrógeno, flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{231} es hidrógeno y R^{230} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0307] En algunas formas de realización de compuestos de la Fórmula Ipp, R^{229} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{229} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{229} es hidrógeno, cloro o metil.

[0308] En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{231} es hidrógeno y R^{230} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{231} es hidrógeno y R^{230} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de

compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{231} es hidrógeno y R^{230} es alquil inferior. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{231} es hidrógeno y R^{230} es C_{1-3} alquil. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{231} es hidrógeno y R^{230} es metil.

[0309] En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es flúor, cloro, bromo. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0310] En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es cicloalquil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos

de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es ciclopropil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es ciclopropil, trifluorometil, metil o etil.

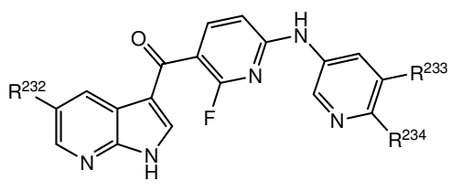
[0311] En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es cicloalquil. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es ciclopropil.

[0312] En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es trifluorometil, metil o etil. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es trifluorometil. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es metil. En algunas formas de realización de compuestos de la

Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es etil.

[0313] En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es C_{1-3} alcoxi. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es metoxi o etoxi. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es metoxi. En algunas formas de realización de compuestos de la Fórmula Ipp, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ipp, R^{230} es hidrógeno y R^{231} es etoxi.

[0314] En un cuadragésimo-segundo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iqq:



Fórmula Iqq

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{232} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{233} es hidrógeno y R^{234} es hidrógeno, flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{234} es hidrógeno y R^{233} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0315] En algunas formas de realización de compuestos de la Fórmula Iqq, R^{232} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{232} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{232} es hidrógeno, cloro o metil.

[0316] En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{234} es hidrógeno y R^{233} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{234} es hidrógeno y R^{233} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{234} es hidrógeno y R^{233} es alquil inferior. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{234} es hidrógeno y R^{233} es C_{1-3} alquil. En algunas formas de realización de compuestos de

la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{234} es hidrógeno y R^{233} es metil.

[0317] En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es flúor, cloro, bromo. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0318] En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es cicloalquil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es ciclopropil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización

antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es ciclopropil, trifluorometil, metil o etil.

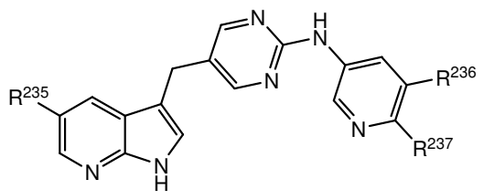
[0319] En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es cicloalquil. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es ciclopropil.

[0320] En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es trifluorometil, metil o etil. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es trifluorometil. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es metil. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es etil.

[0321] En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Iqq, R^{233} es hidrógeno y R^{234} es alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es C_{1-3} alcoxi. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es metoxi o etoxi. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es metoxi. En algunas formas de realización de compuestos de la Fórmula Iqq, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iqq, R^{233} es hidrógeno y R^{234} es etoxi.

[0322] En un cuadragésimo-tercero aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Irr:



Fórmula Irr

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{235} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{236} es hidrógeno y R^{237} es hidrógeno, flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{237} es hidrógeno y R^{236} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0323] En algunas formas de realización de compuestos de la Fórmula Irr, R^{235} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{235} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{235} es hidrógeno, cloro o metil.

[0324] En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{237} es hidrógeno y R^{236} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{237} es hidrógeno y R^{236} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{237} es hidrógeno y R^{236} es alquil inferior. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{237} es hidrógeno y R^{236} es C_{1-3} alquil. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{237} es hidrógeno y R^{236} es metil.

[0325] En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es flúor, cloro, bromo. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0326] En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es cicloalquil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es ciclopropil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es ciclopropil, trifluorometil, metil o etil.

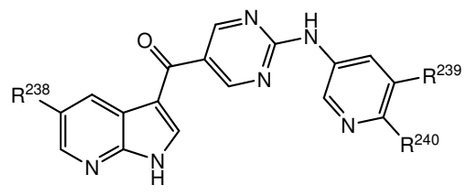
[0327] En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es cicloalquil. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es ciclopropil.

[0328] En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es trifluorometil, metil o etil. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es trifluorometil. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es metil. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es etil.

[0329] En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Irr,

adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es C_{1-3} alcoxi. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es metoxi o etoxi. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es metoxi. En algunas formas de realización de compuestos de la Fórmula Irr, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Irr, R^{236} es hidrógeno y R^{237} es etoxi.

[0330] En un cuadragésimo-cuarto aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iss:



Fórmula Iss

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{238} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{239} es hidrógeno y R^{240} es hidrógeno, flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{240} es hidrógeno y R^{239} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0331] En algunas formas de realización de compuestos de la Fórmula Iss, R^{238} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{238} es hidrógeno, cloro o C_{1-3} alquil. En una de las formas de realización, R^{238} es hidrógeno, cloro o metil.

[0332] En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{240} es hidrógeno y R^{239} es flúor, cloro, bromo, cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{240} es hidrógeno y R^{239} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{240} es hidrógeno y R^{239} es alquil inferior. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{240} es hidrógeno y R^{239} es C_{1-3} alquil. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{240} es hidrógeno y R^{239} es metil.

[0333] En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es flúor, cloro, bromo, cicloalquil, alquil inferior

sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es flúor, cloro, bromo. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es cicloalquil, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0334] En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es cicloalquil o alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es cicloalquil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es ciclopropil o C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es ciclopropil, trifluorometil, metil o etil.

[0335] En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es cicloalquil. En algunas formas de realización de

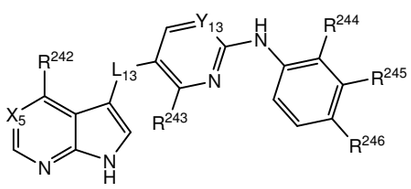
compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es ciclopropil.

[0336] En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es alquil inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es C_{1-3} alquil sustituido opcionalmente con 1, 2, o 3 flúor. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es trifluorometil, metil o etil. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es trifluorometil. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es metil. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es etil.

[0337] En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización

antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es C_{1-3} alcoxi. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es metoxi o etoxi. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es metoxi. En algunas formas de realización de compuestos de la Fórmula Iss, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iss, R^{239} es hidrógeno y R^{240} es etoxi.

[0338] En un cuadragésimo-quinto aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Itt:



Fórmula Itt

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

X_5 es –N=, -C(H)=, o -C(R^{241})= ;

Y_{13} es –N= y R^{243} es hidrógeno; o Y_{13} es -C(H)= y R^{243} es flúor;

L_{13} es -C(H_2)- o -C(O)-;

Donde X_5 es -C(R^{241})=, R^{242} es hidrógeno;

Donde X_5 es –N= o -C(H)=, R^{242} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{247}, y -O-R^{248};

R^{241} es flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{244} y R^{245} son hidrógeno y R^{246} se selecciona del grupo que consiste de flúor, cloro, -O-R^{249}, -S-R^{250}, -S(O_2)-R^{251}, y alquil inferior sustituido opcionalmente con una o más R^{252}; o

R^{244} y R^{246} son hidrógeno y R^{245} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{245} y R^{246} son hidrógeno y R^{244} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{244} es hidrógeno, R^{245} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{246} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{247} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{248} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior;

R^{249}, R^{250} y R^{251} son alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{252} es flúor, -OH, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0339] En algunas formas de realización de compuestos de la Fórmula Itt, X_5 es –N= y R^{242} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{247}, y -O-R^{248}. En una de las formas de realización, X_5 es –N= y R^{242} se selecciona del grupo que consiste de

cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, X_5 es –N= y R^{242} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, X_5 es -N= y R^{242} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

[0340] En algunas formas de realización de compuestos de la Fórmula Itt, X_5 es -C(H)= o -C(R^{241})= y R^{241} es flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor. En una de las formas de realización, X_5 es -C(H)= o -C(R^{241})= y R^{241} es cloro o alquil inferior. En una de las formas de realización, X_5 es -C(H)= o -C(R^{241})= y R^{241} es cloro o C_{1-3} alquil. En una de las formas de realización, X_5 es -C(H)= o -C(R^{241})= y R^{241} es cloro o metil.

[0341] En algunas formas de realización de compuestos de la Fórmula Itt, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Itt, R^{244} y R^{245} son hidrógeno y R^{246} se selecciona del grupo que consiste de flúor, cloro, -O-R^{249}, -S-R^{250}, -S(O_2)-R^{251}, y alquil inferior sustituido opcionalmente con una o más R^{252}. En algunas formas de realización de compuestos de la Fórmula Itt, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Itt, R^{244} y R^{245} son hidrógeno y R^{246} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior y alquil inferior sustituido opcionalmente con uno o más flúor o -OH. En algunas formas de realización de compuestos de la Fórmula Itt, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Itt, R^{244} y R^{245} son hidrógeno y R^{246} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior, y alquil inferior.

[0342] En algunas formas de realización de compuestos de la Fórmula Itt, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Itt, R^{244} y R^{246} son hidrógeno y R^{245} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Itt, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Itt, R^{244} y R^{246} son hidrógeno y R^{245} es flúor, cloro, alquil inferior o alcoxi inferior.

[0343] En algunas formas de realización de compuestos de la Fórmula Itt, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Itt, R^{245} y R^{246} son hidrógeno y R^{244} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Itt, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Itt, R^{245} y R^{246} son hidrógeno y R^{244} es flúor, cloro, alquil inferior o alcoxi inferior.

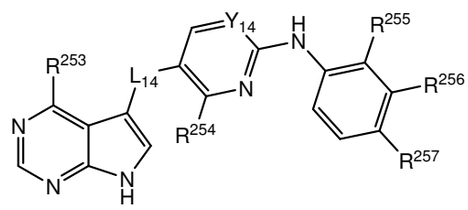
[0344] En algunas formas de realización de compuestos de la Fórmula Itt, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Itt, R^{244} es hidrógeno, R^{245} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{246} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Itt, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Itt, R^{244} es hidrógeno, R^{245} es flúor, cloro, alquil inferior o alcoxi inferior y R^{246} es flúor, cloro, alquil inferior o alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Itt, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Itt, R^{244} es hidrógeno, R^{245} es flúor, cloro, o alcoxi inferior y R^{246} es flúor, cloro, o alcoxi inferior.

[0345] En algunas formas de realización de compuestos de la Fórmula Itt, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Itt, L_{13} es -C(H_2)-. En algunas formas de realización de compuestos de la Fórmula Itt, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Itt, L_{13} es -C(O)-.

[0346] En algunas formas de realización de compuestos de la Fórmula Itt, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Itt, Y_{13} es –N= y R^{243} es hidrógeno. En algunas formas de realización de compuestos de la Fórmula Itt, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Itt, Y_{13} es -C(H)= y R^{243} es flúor.

[0347] En un cuadragésimo-sexto aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iuu:



Fórmula Iuu

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Y_{14} es –N= y R^{254} es hidrógeno; o Y_{14} es -C(H)= y R^{254} es flúor;

L_{14} es -C(H_2)- o -C(O)-;

R^{253} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{258} y -O-R^{259};

R^{255} y R^{256} son hidrógeno y R^{257} se selecciona del grupo que consiste de flúor, cloro, -O-R^{260}, -S-R^{261}, -S(O_2)-R^{262}, y alquil inferior sustituido opcionalmente con una o más R^{263}; o

R^{255} y R^{257} son hidrógeno y R^{256} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{256} y R^{257} son hidrógeno y R^{255} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{255} es hidrógeno, R^{256} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{257} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{258} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{259} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior;

R^{260}, R^{261} y R^{262} son alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{263} es flúor, -OH, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0348] En algunas formas de realización de compuestos de la Fórmula Iuu, R^{253} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{253} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi y

C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{253} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

[0349] En algunas formas de realización de compuestos de la Fórmula Iuu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iuu, R^{255} y R^{256} son hidrógeno y R^{257} se selecciona del grupo que consiste de flúor, cloro, -O-R^{260}, -S-R^{261}, -S(O_2)-R^{262}, y alquil inferior sustituido opcionalmente con una o más R^{263}. En algunas formas de realización de compuestos de la Fórmula Iuu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iuu, R^{255} y R^{256} son hidrógeno y R^{257} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior y alquil inferior sustituido opcionalmente con uno o más flúor o -OH. En algunas formas de realización de compuestos de la Fórmula Iuu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iuu, R^{255} y R^{256} son hidrógeno y R^{257} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior, y alquil inferior.

[0350] En algunas formas de realización de compuestos de la Fórmula Iuu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iuu, R^{255} y R^{257} son hidrógeno y R^{256} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iuu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iuu, R^{255} y R^{257} son hidrógeno y R^{256} es flúor, cloro, alquil inferior o alcoxi inferior.

[0351] En algunas formas de realización de compuestos de la Fórmula Iuu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Iuu, R^{256} y R^{257} son hidrógeno y R^{255} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iuu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iuu, R^{256} y R^{257} son hidrógeno y R^{255} es flúor, cloro, alquil inferior o alcoxi inferior.

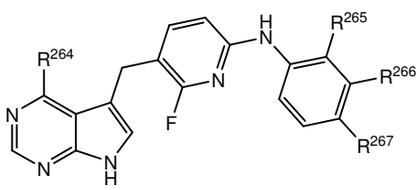
[0352] En algunas formas de realización de compuestos de la Fórmula Iuu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iuu, R^{255} es hidrógeno, R^{256} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{257} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iuu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iuu, R^{255} es hidrógeno, R^{256} es flúor, cloro, alquil inferior o alcoxi inferior y R^{257} es flúor, cloro, alquil inferior o alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Iuu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iuu, R^{255} es hidrógeno, R^{256} es flúor, cloro, o alcoxi inferior y R^{257} es flúor, cloro, o alcoxi inferior.

[0353] En algunas formas de realización de compuestos de la Fórmula Iuu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iuu, L_{14} es $-C(H_2)-$. En algunas formas de realización de compuestos de la Fórmula Iuu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iuu, L_{14} es -C(O)-.

[0354] En algunas formas de realización de compuestos de la Fórmula Iuu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Iuu, Y_{14} es –N= y R^{254} es hidrógeno. En algunas formas de realización de compuestos de la Fórmula Iuu, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iuu, Y_{14} es -C(H)= y R^{254} es flúor.

[0355] En un cuadragésimo-séptimo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ivv:



Fórmula Ivv

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{264} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{268} y -O-R^{269};

R^{265} y R^{266} son hidrógeno y R^{267} se selecciona del grupo que consiste de flúor, cloro, -O-R^{270}, -S-R^{271}, -S(O_2)-R^{272}, y alquil inferior sustituido opcionalmente con una o más R^{273}; o

R^{265} y R^{267} son hidrógeno y R^{266} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{266} y R^{267} son hidrógeno y R^{265} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{265} es hidrógeno, R^{266} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{267} es flúor, cloro, alquil inferior sustituido opcionalmente con

uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{268} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{269} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior;

R^{270}, R^{271} y R^{272} son alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{273} es flúor, -OH, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0356] En algunas formas de realización de compuestos de la Fórmula Ivv, R^{264} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{264} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{264} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

[0357] En algunas formas de realización de compuestos de la Fórmula Ivv, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ivv, R^{265} y R^{266} son hidrógeno y R^{267} se selecciona del grupo que consiste de flúor, cloro, -O-R^{270}, -S-R^{271}, -S(O_2)-R^{272}, y alquil inferior sustituido opcionalmente con una o más R^{273}. En algunas formas de realización de compuestos de la Fórmula Ivv, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ivv, R^{265} y R^{266} son hidrógeno y R^{267} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior, y alquil inferior sustituido opcionalmente con uno o más flúor o -OH. En algunas formas de

realización de compuestos de la Fórmula Ivv, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ivv, R^{265} y R^{266} son hidrógeno y R^{267} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior, y alquil inferior.

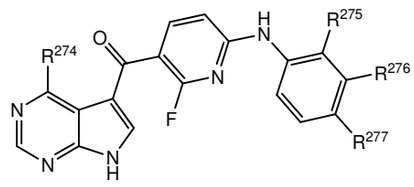
[0358] En algunas formas de realización de compuestos de la Fórmula Ivv, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ivv, R^{265} y R^{267} son hidrógeno y R^{266} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ivv, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ivv, R^{265} y R^{267} son hidrógeno y R^{266} es flúor, cloro, alquil inferior o alcoxi inferior.

[0359] En algunas formas de realización de compuestos de la Fórmula Ivv, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ivv, R^{266} y R^{267} son hidrógeno y R^{265} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ivv, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ivv, R^{266} y R^{267} son hidrógeno y R^{265} es flúor, cloro, alquil inferior o alcoxi inferior.

[0360] En algunas formas de realización de compuestos de la Fórmula Ivv, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ivv, R^{265} es hidrógeno, R^{266} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{267} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ivv, adicional a cualquiera de las formas de

realización antes mencionadas de la Fórmula Ivv, R^{265} es hidrógeno, R^{266} es flúor, cloro, alquil inferior o alcoxi inferior y R^{267} es flúor, cloro, alquil inferior o alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Ivv, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ivv, R^{265} es hidrógeno, R^{266} es flúor, cloro, o alcoxi inferior y R^{267} es flúor, cloro, o alcoxi inferior.

[0361] En un cuadragésimo-octavo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iww:



Fórmula Iww

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{274} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{278} y -O-R^{279};

R^{275} y R^{276} son hidrógeno y R^{277} se selecciona del grupo que consiste de flúor, cloro, -O-R^{280}, -S-R^{281}, -S(O_2)-R^{282} y alquil inferior sustituido opcionalmente con una o más R^{283}; o

R^{275} y R^{277} son hidrógeno y R^{276} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{276} y R^{277} son hidrógeno y R^{275} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{275} es hidrógeno, R^{276} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{277} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{278} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{279} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior;

R^{280}, R^{281} y R^{282} son alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{283} es flúor, -OH, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0362] En algunas formas de realización de compuestos de la Fórmula Iww, R^{274} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{274} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{274} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

[0363] En algunas formas de realización de compuestos de la Fórmula Iww, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iww, R^{275} y R^{276} son hidrógeno y R^{277} se selecciona del grupo que consiste de flúor, cloro, -O-R^{280}, -S-R^{281}, -S(O_2)-R^{282}, y alquil inferior sustituido opcionalmente con una o más R^{283}. En algunas formas de realización de compuestos de la Fórmula Iww, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Iww, R^{275} y R^{276} son hidrógeno y R^{277} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior, y alquil inferior sustituido opcionalmente con uno o más flúor o -OH. En algunas formas de realización de compuestos de la Fórmula Iww, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iww, R^{275} y R^{276} son hidrógeno y R^{277} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior, y alquil inferior.

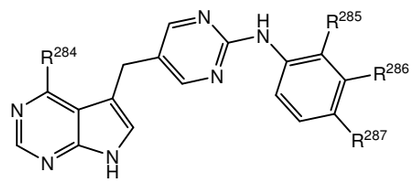
[0364] En algunas formas de realización de compuestos de la Fórmula Iww, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iww, R^{275} y R^{277} son hidrógeno y R^{276} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iww, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iww, R^{275} y R^{277} son hidrógeno y R^{276} es flúor, cloro, alquil inferior o alcoxi inferior.

[0365] En algunas formas de realización de compuestos de la Fórmula Iww, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iww, R^{276} y R^{277} son hidrógeno y R^{275} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iww, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iww, R^{276} y R^{277} son hidrógeno y R^{275} es flúor, cloro, alquil inferior o alcoxi inferior.

[0366] En algunas formas de realización de compuestos de la Fórmula Iww, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Iww, R^{275} es hidrógeno, R^{276} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{277} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iww, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iww, R^{275} es hidrógeno, R^{276} es flúor, cloro, alquil inferior o alcoxi inferior y R^{277} es flúor, cloro, alquil inferior o alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Iww, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iww, R^{275} es hidrógeno, R^{276} es flúor, cloro, o alcoxi inferior y R^{277} es flúor, cloro, o alcoxi inferior.

[0367] En un cuadragésimo-noveno aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Ixx:



Fórmula Ixx

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{284} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{288} y -O-R^{289};

R^{285} y R^{286} son hidrógeno y R^{287} se selecciona del grupo que consiste de flúor, cloro, -O-R^{290}, -S-R^{291}, -S(O_2)-R^{292}, y alquil inferior sustituido opcionalmente con una o más R^{293}; o

R^{285} y R^{287} son hidrógeno y R^{286} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{286} y R^{287} son hidrógeno y R^{285} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{285} es hidrógeno, R^{286} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{287} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{288} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{289} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior;

R^{290}, R^{291} y R^{292} son alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{293} es flúor, -OH, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0368] En algunas formas de realización de compuestos de la Fórmula Ixx, R^{284} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior, y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{284} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi, y C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{284} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi, y 2-metoxi-etoxi.

[0369] En algunas formas de realización de compuestos de la Fórmula Ixx, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ixx, R^{285} y R^{286} son hidrógeno y R^{287} se selecciona del grupo que consiste de flúor, cloro, -O-R^{290}, -S-R^{291}, -S(O_2)-R^{292} y alquil inferior sustituido opcionalmente con una o más R^{293}. En algunas formas de realización de compuestos de la Fórmula Ixx, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ixx, R^{285} y R^{286} son hidrógeno y R^{287} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior y alquil inferior sustituido opcionalmente con uno o más flúor o -OH. En algunas formas de realización de compuestos de la Fórmula Ixx, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ixx, R^{285} y R^{286} son hidrógeno y R^{287} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior y alquil inferior.

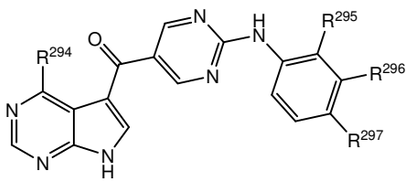
[0370] En algunas formas de realización de compuestos de la Fórmula Ixx, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ixx, R^{285} y R^{287} son hidrógeno y R^{286} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ixx, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ixx, R^{285} y R^{287} son hidrógeno y R^{286} es flúor, cloro, alquil inferior o alcoxi inferior.

[0371] En algunas formas de realización de compuestos de la Fórmula Ixx, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ixx, R^{286} y R^{287} son hidrógeno y R^{285} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ixx,

adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ixx, R^{286} y R^{287} son hidrógeno y R^{285} es flúor, cloro, alquil inferior o alcoxi inferior.

[0372] En algunas formas de realización de compuestos de la Fórmula Ixx, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ixx, R^{285} es hidrógeno, R^{286} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{287} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Ixx, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ixx, R^{285} es hidrógeno, R^{286} es flúor, cloro, alquil inferior o alcoxi inferior y R^{287} es flúor, cloro, alquil inferior o alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Ixx, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Ixx, R^{285} es hidrógeno, R^{286} es flúor, cloro, o alcoxi inferior y R^{287} es flúor, cloro, o alcoxi inferior.

[0373] En un quincuagésimo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iyy:



Fórmula Iyy

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{294} se selecciona del grupo que consiste de hidrógeno, cicloalquil, alquil inferior sustituido opcionalmente con una o más R^{298} y -O-R^{299};

R^{295} y R^{296} son hidrógeno y R^{297} se selecciona del grupo que consiste de flúor, cloro, -O-R^{300}, -S-R^{301}, -S(O_2)-R^{302} y alquil inferior sustituido opcionalmente con una o más R^{303}; o

R^{295} y R^{297} son hidrógeno y R^{296} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{296} y R^{297} son hidrógeno y R^{295} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{295} es hidrógeno, R^{296} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{297} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{298} es flúor o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{299} es alquil inferior, alquil inferior sustituido con uno o más flúor, o alquil inferior sustituido con alcoxi inferior;

R^{300}, R^{301} y R^{302} son alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{303} es flúor, -OH, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0374] En algunas formas de realización de compuestos de la Fórmula Iyy, R^{294} se selecciona del grupo que consiste de cicloalquil, alquil inferior, alcoxi inferior y alcoxi inferior sustituido con alcoxi inferior. En una de las formas de realización, R^{294} se selecciona del grupo que consiste de C_{3-6} cicloalquil, C_{1-3} alquil, C_{1-3} alcoxi y

C_{1-3} alcoxi sustituido con C_{1-3} alcoxi. En una de las formas de realización, R^{294} se selecciona del grupo que consiste de metil, ciclopropil, metoxi, etoxi y 2-metoxi-etoxi.

[0375] En algunas formas de realización de compuestos de la Fórmula Iyy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iyy, R^{295} y R^{296} son hidrógeno y R^{297} se selecciona del grupo que consiste de flúor, cloro, -O-R^{300}, -S-R^{301}, -S(O_2)-R^{302} y alquil inferior sustituido opcionalmente con una o más R^{303}. En algunas formas de realización de compuestos de la Fórmula Iyy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iyy, R^{295} y R^{296} son hidrógeno y R^{297} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior y alquil inferior sustituido opcionalmente con uno o más flúor o -OH. En algunas formas de realización de compuestos de la Fórmula Iyy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iyy, R^{295} y R^{296} son hidrógeno y R^{297} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior, y alquil inferior.

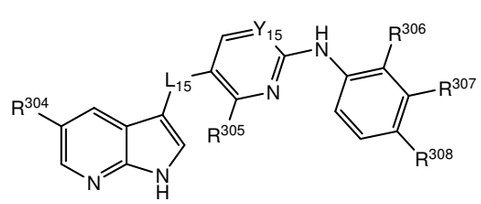
[0376] En algunas formas de realización de compuestos de la Fórmula Iyy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iyy, R^{295} y R^{297} son hidrógeno y R^{296} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iyy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iyy, R^{295} y R^{297} son hidrógeno y R^{296} es flúor, cloro, alquil inferior o alcoxi inferior.

[0377] En algunas formas de realización de compuestos de la Fórmula Iyy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Iyy, R^{296} y R^{297} son hidrógeno y R^{295} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iyy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iyy, R^{296} y R^{297} son hidrógeno y R^{295} es flúor, cloro, alquil inferior o alcoxi inferior.

[0378] En algunas formas de realización de compuestos de la Fórmula Iyy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iyy, R^{295} es hidrógeno, R^{296} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{297} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iyy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iyy, R^{295} es hidrógeno, R^{296} es flúor, cloro, alquil inferior o alcoxi inferior y R^{297} es flúor, cloro, alquil inferior o alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Iyy, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iyy, R^{295} es hidrógeno, R^{296} es flúor, cloro, o alcoxi inferior y R^{297} es flúor, cloro, o alcoxi inferior.

[0379] En un quincuagésimo-primero aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Izz:



Fórmula Izz

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

Y_{15} es –N= y R^{305} es hidrógeno; o Y_{15} es -C(H)= y R^{305} es flúor;

L_{15} es -$C(H_2)$- o -C(O)-;

R^{304} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{306} y R^{307} son hidrógeno y R^{308} se selecciona del grupo que consiste de flúor, cloro, -O-R^{309}, -S-R^{310}, -S(O_2)-R^{311} y alquil inferior sustituido opcionalmente con una o más R^{312}; o

R^{306} y R^{308} son hidrógeno y R^{307} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{307} y R^{308} son hidrógeno y R^{306} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{306} es hidrógeno, R^{307} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{308} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{309}, R^{310} y R^{311} son alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{312} es flúor, -OH, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0380] En algunas formas de realización de compuestos de la Fórmula Izz, R^{304} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{304} es cloro o C_{1-3} alquil. En una de las formas de realización, R^{304} es cloro o metil.

[0381] En algunas formas de realización de compuestos de la Fórmula Izz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Izz, R^{306} y R^{307} son hidrógeno y R^{308} se selecciona del grupo que consiste de flúor, cloro, -O-R^{309}, -S-R^{310}, -S(O_2)-R^{311} y alquil inferior sustituido opcionalmente con una o más R^{312}. En algunas formas de realización de compuestos de la Fórmula Izz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Izz, R^{306} y R^{307} son hidrógeno y R^{308} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior, y alquil inferior sustituido opcionalmente con uno o más flúor o -OH. En algunas formas de realización de compuestos de la Fórmula Izz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Izz, R^{306} y R^{307} son hidrógeno y R^{308} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior, y alquil inferior.

[0382] En algunas formas de realización de compuestos de la Fórmula Izz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Izz, R^{306} y R^{308} son hidrógeno y R^{307} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Izz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Izz, R^{306} y R^{308} son hidrógeno y R^{307} es flúor, cloro, alquil inferior o alcoxi inferior.

[0383] En algunas formas de realización de compuestos de la Fórmula Izz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Izz, R^{307} y R^{308} son hidrógeno y R^{306} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Izz,

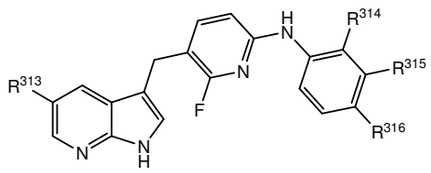
adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Izz, R^{307} y R^{308} son hidrógeno y R^{306} es flúor, cloro, alquil inferior o alcoxi inferior.

[0384] En algunas formas de realización de compuestos de la Fórmula Izz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Izz, R^{306} es hidrógeno, R^{307} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{308} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Izz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Izz, R^{306} es hidrógeno, R^{307} es flúor, cloro, alquil inferior o alcoxi inferior y R^{308} es flúor, cloro, alquil inferior o alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Izz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Izz, R^{306} es hidrógeno, R^{307} es flúor, cloro, o alcoxi inferior y R^{308} es flúor, cloro, o alcoxi inferior.

[0385] En algunas formas de realización de compuestos de la Fórmula Izz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Izz, L_{15} es -C(H_2)-. En algunas formas de realización de compuestos de la Fórmula Izz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Izz, L_{15} es -C(O)-.

[0386] En algunas formas de realización de compuestos de la Fórmula Izz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Izz, Y_{15} es –N= y R^{305} es hidrógeno. En algunas formas de realización de compuestos de la Fórmula Izz, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Izz, Y_{15} es -C(H)= y R^{305} es flúor.

[0387] En un quincuagésimo-segundo aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iab:



Fórmula Iab

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{313} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{314} y R^{315} son hidrógeno y R^{316} se selecciona del grupo que consiste de flúor, cloro, -O-R^{317}, -S-R^{318}, -S(O_2)-R^{319} y alquil inferior sustituido opcionalmente con una o más R^{320}; o

R^{314} y R^{316} son hidrógeno y R^{315} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{315} y R^{316} son hidrógeno y R^{314} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{314} es hidrógeno, R^{315} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{316} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{317}, R^{318} y R^{319} son alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{320} es flúor, -OH, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0388] En algunas formas de realización de compuestos de la Fórmula Iab, R^{313} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{313} es cloro o C_{1-3} alquil. En una de las formas de realización, R^{313} es cloro o metil.

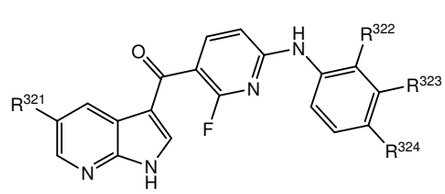
[0389] En algunas formas de realización de compuestos de la Fórmula Iab, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iab, R^{314} y R^{315} son hidrógeno y R^{316} se selecciona del grupo que consiste de flúor, cloro, -O-R^{317}, -S-R^{318}, -S(O_2)-R^{319} y alquil inferior sustituido opcionalmente con una o más R^{320}. En algunas formas de realización de compuestos de la Fórmula Iab, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iab, R^{314} y R^{315} son hidrógeno y R^{316} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior y alquil inferior sustituido opcionalmente con uno o más flúor o -OH. En algunas formas de realización de compuestos de la Fórmula Iab, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iab, R^{314} y R^{315} son hidrógeno y R^{316} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior y alquil inferior.

[0390] En algunas formas de realización de compuestos de la Fórmula Iab, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iab, R^{314} y R^{316} son hidrógeno y R^{315} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iab, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iab, R^{314} y R^{316} son hidrógeno y R^{315} es flúor, cloro, alquil inferior o alcoxi inferior.

[0391] En algunas formas de realización de compuestos de la Fórmula Iab, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iab, R^{315} y R^{316} son hidrógeno y R^{314} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iab, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iab, R^{315} y R^{316} son hidrógeno y R^{314} es flúor, cloro, alquil inferior o alcoxi inferior.

[0392] En algunas formas de realización de compuestos de la Fórmula Iab, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iab, R^{314} es hidrógeno, R^{315} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{316} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iab, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iab, R^{314} es hidrógeno, R^{315} es flúor, cloro, alquil inferior o alcoxi inferior y R^{316} es flúor, cloro, alquil inferior o alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Iab, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iab, R^{314} es hidrógeno, R^{315} es flúor, cloro, o alcoxi inferior y R^{316} es flúor, cloro, o alcoxi inferior.

[0393] En un quincuagésimo-tercero aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iac:



Fórmula Iac

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{321} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{322} y R^{323} son hidrógeno y R^{324} se selecciona del grupo que consiste de flúor, cloro, -O-R^{325}, -S-R^{326}, -S(O_2)-R^{327} y alquil inferior sustituido opcionalmente con una o más R^{328}; o

R^{322} y R^{324} son hidrógeno y R^{323} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{323} y R^{324} son hidrógeno y R^{322} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{322} es hidrógeno, R^{323} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{324} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{325}, R^{326} y R^{327} son alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{328} es flúor, -OH, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0394] En algunas formas de realización de compuestos de la Fórmula Iac, R^{321} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{321} es cloro o C_{1-3} alquil. En una de las formas de realización, R^{321} es cloro o metil.

[0395] En algunas formas de realización de compuestos de la Fórmula Iac, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iac, R^{322} y R^{323} son hidrógeno y R^{324} se selecciona del grupo que consiste de flúor, cloro, -O-R^{325}, -S-R^{326}, -S(O_2)-R^{327} y alquil inferior sustituido opcionalmente con una o más R^{328}. En algunas formas de realización de compuestos de la Fórmula Iac, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iac, R^{322} y R^{323} son hidrógeno y R^{324} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior y alquil inferior sustituido opcionalmente con uno o más flúor o -OH. En algunas formas de realización de compuestos de la Fórmula Iac, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iac, R^{322} y R^{323} son hidrógeno y R^{324} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior, y alquil inferior.

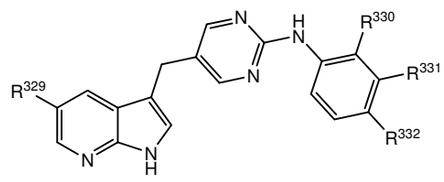
[0396] En algunas formas de realización de compuestos de la Fórmula Iac, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iac, R^{322} y R^{324} son hidrógeno y R^{323} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iac, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iac, R^{322} y R^{324} son hidrógeno y R^{323} es flúor, cloro, alquil inferior o alcoxi inferior.

[0397] En algunas formas de realización de compuestos de la Fórmula Iac, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iac, R^{323} y R^{324} son hidrógeno y R^{322} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iac,

adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iac, R^{323} y R^{324} son hidrógeno y R^{322} es flúor, cloro, alquil inferior o alcoxi inferior.

[0398] En algunas formas de realización de compuestos de la Fórmula Iac, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iac, R^{322} es hidrógeno, R^{323} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{324} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iac, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iac, R^{322} es hidrógeno, R^{323} es flúor, cloro, alquil inferior o alcoxi inferior y R^{324} es flúor, cloro, alquil inferior o alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Iac, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iac, R^{322} es hidrógeno, R^{323} es flúor, cloro, o alcoxi inferior y R^{324} es flúor, cloro, o alcoxi inferior.

[0399] En un quincuagésimo-cuarto aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula Iad:



Fórmula Iad

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{329} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{330} y R^{331} son hidrógeno y R^{332} se selecciona del grupo que consiste de flúor, cloro, -O-R^{333}, -S-R^{334}, -S(O_2)-R^{335} y alquil inferior sustituido opcionalmente con una o más R^{336}; o

R^{330} y R^{332} son hidrógeno y R^{331} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{331} y R^{332} son hidrógeno y R^{330} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{330} es hidrógeno, R^{331} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{332} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{333}, R^{334} y R^{335} son alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{336} es flúor, -OH, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0400] En algunas formas de realización de compuestos de la Fórmula Iad, R^{329} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{329} es cloro o C_{1-3} alquil. En una de las formas de realización, R^{329} es cloro o metil.

[0401] En algunas formas de realización de compuestos de la Fórmula Iad, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iad, R^{330} y R^{331} son hidrógeno y R^{332} se selecciona del grupo que consiste de flúor, cloro, -O-R^{333}, -S-R^{334}, -S(O_2)-R^{335} y alquil inferior sustituido opcionalmente con

una o más R^{336}. En algunas formas de realización de compuestos de la Fórmula Iad, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iad, R^{330} y R^{331} son hidrógeno y R^{332} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior, y alquil inferior sustituido opcionalmente con uno o más flúor o -OH. En algunas formas de realización de compuestos de la Fórmula Iad, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iad, R^{330} y R^{331} son hidrógeno y R^{332} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior y alquil inferior.

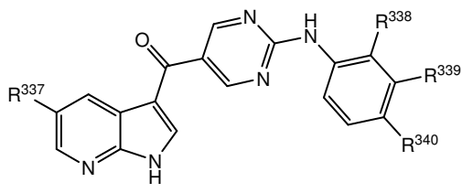
[0402] En algunas formas de realización de compuestos de la Fórmula Iad, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iad, R^{330} y R^{332} son hidrógeno y R^{331} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iad, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iad, R^{330} y R^{332} son hidrógeno y R^{331} es flúor, cloro, alquil inferior o alcoxi inferior.

[0403] En algunas formas de realización de compuestos de la Fórmula Iad, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iad, R^{331} y R^{332} son hidrógeno y R^{330} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iad, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iad, R^{331} y R^{332} son hidrógeno y R^{330} es flúor, cloro, alquil inferior o alcoxi inferior.

[0404] En algunas formas de realización de compuestos de la Fórmula Iad, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula

Iad, R^{330} es hidrógeno, R^{331} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{332} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iad, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iad, R^{330} es hidrógeno, R^{331} es flúor, cloro, alquil inferior o alcoxi inferior y R^{332} es flúor, cloro, alquil inferior o alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Iad, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iad, R^{330} es hidrógeno, R^{331} es flúor, cloro, o alcoxi inferior y R^{332} es flúor, cloro, o alcoxi inferior.

[0405] En un quincuagésimo-quinto aspecto, se proporcionan los compuestos de la Fórmula I que tienen la estructura de acuerdo con la siguiente Fórmula:



Fórmula Iae

O una sal, profármaco, solvato, tautómero o esteroisómero del mismo, donde:

R^{337} es hidrógeno, flúor, cloro, o alquil inferior sustituido opcionalmente con uno o más flúor;

R^{338} y R^{339} son hidrógeno y R^{340} se selecciona del grupo que consiste de flúor, cloro, -O-R^{341}, -S-R^{342}, -S(O_2)-R^{343} y alquil inferior sustituido opcionalmente con una o más R^{344}; o

R^{338} y R^{340} son hidrógeno y R^{339} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{339} y R^{340} son hidrógeno y R^{338} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor; o

R^{338} es hidrógeno, R^{339} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{340} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor;

R^{341}, R^{342} y R^{343} son alquil inferior sustituido opcionalmente con uno o más flúor; y

R^{344} es flúor, -OH, o alcoxi inferior sustituido opcionalmente con uno o más flúor.

[0406] En algunas formas de realización de compuestos de la Fórmula Iae, R^{337} es hidrógeno, cloro o alquil inferior. En una de las formas de realización, R^{337} es cloro o C_{1-3} alquil. En una de las formas de realización, R^{337} es cloro o metil.

[0407] En algunas formas de realización de compuestos de la Fórmula Iae, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iae, R^{338} y R^{339} son hidrógeno y R^{340} se selecciona del grupo que consiste de flúor, cloro, -O-R^{341}, -S-R^{342}, -S(O_2)-R^{343}, y alquil inferior sustituido opcionalmente con una o más R^{344}. En algunas formas de realización de compuestos de la Fórmula Iae, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iae, R^{338} y R^{339} son hidrógeno y R^{340} se selecciona del grupo que consiste de flúor,

cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior y alquil inferior sustituido opcionalmente con uno o más flúor o -OH. En algunas formas de realización de compuestos de la Fórmula Iae, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iae, R^{338} y R^{339} son hidrógeno y R^{340} se selecciona del grupo que consiste de flúor, cloro, alcoxi inferior, alquiltio inferior, alquilsulfonilo inferior y alquil inferior.

[0408] En algunas formas de realización de compuestos de la Fórmula Iae, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iae, R^{338} y R^{340} son hidrógeno y R^{339} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iae, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iae, R^{338} y R^{340} son hidrógeno y R^{339} es flúor, cloro, alquil inferior o alcoxi inferior.

[0409] En algunas formas de realización de compuestos de la Fórmula Iae, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iae, R^{339} y R^{340} son hidrógeno y R^{338} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iae, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iae, R^{339} y R^{340} son hidrógeno y R^{338} es flúor, cloro, alquil inferior o alcoxi inferior.

[0410] En algunas formas de realización de compuestos de la Fórmula Iae, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iae, R^{338} es hidrógeno, R^{339} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o alcoxi inferior sustituido opcionalmente con uno o más flúor y R^{340} es flúor, cloro, alquil inferior sustituido opcionalmente con uno o más flúor, o

alcoxi inferior sustituido opcionalmente con uno o más flúor. En algunas formas de realización de compuestos de la Fórmula Iae, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iae, R^{338} es hidrógeno, R^{339} es flúor, cloro, alquil inferior o alcoxi inferior y R^{340} es flúor, cloro, alquil inferior o alcoxi inferior. En algunas formas de realización de compuestos de la Fórmula Iae, adicional a cualquiera de las formas de realización antes mencionadas de la Fórmula Iae, R^{338} es hidrógeno, R^{339} es flúor, cloro, o alcoxi inferior y R^{340} es flúor, cloro, o alcoxi inferior.

[0411] En una de las formas de realización de los compuestos de la Fórmula I, el compuesto se selecciona del grupo que consiste de los descritos en la Tabla 1.

Tabla 1

[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-ciclohexil-amina (**P-3001**),

[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-ciclopentil-amina (**P-3003**),

[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4,4-difluoro-ciclohexil)-amina (**P-3004**),

[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-ciclopropil-amina (**P-3005**),

[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-cicloheptil-amina (**P-3006**),

[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-ciclobutil-amina

(**P-3007**),

Ciclohexil-[6-fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3008**),

[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4-metil-ciclohexil)-amina (**P-3009**),

(4-Fluoro-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3010**),

(4-Cloro-fenil)-[5-(5-cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3011**),

[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4-fluoro-fenil)-amina (**P-3012**),

[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-6-fluoro-piridina-2-il]-(4,4-difluoro-ciclohexil)-amina (**P-3013**),

[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(2-fluoro-fenil)-amina (**P-3014**),

(2-Cloro-fenil)-[5-(5-cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3015**),

[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(2-metoxi-fenil)-amina (**P-3016**),

[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(3-fluoro-fenil)-amina (**P-3017**),

[5-(5-Metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(6-trifluorometil-piridina-3-il)-amina (**P-3018**),

[6-Fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-3019**),

(6-Metoxi-piridina-3-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3020**),

(4-Metoxi-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3021**),

(4-Fluoro-3-metoxi-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3022**),

(3-Fluoro-4-metoxi-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3023**),

[5-(5-Metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4-propoxi-fenil)-amina (**P-3024**),

(4-Etil-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3025**),

(4-Etoxi-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3026**),

(6-Etoxi-piridina-3-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3027**),

[5-(4-Fluoro-fenil)-2H-pirazol-3-il]-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3028**),

(5-tert-butil-2H-pirazol-3-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3029**),

(4-tert-butil-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3030**),

1,1,1,3,3,3-Hexafluoro-2-{4-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-ilamino]-fenil}-propan-2-ol (**P-3031**),

(5-Ciclopropil-2H-pirazol-3-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-

pirimidina-2-il]-amina (**P-3032**),

[5-(5-Metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4-metilsulfonil-fenil)-amina (**P-3033**),

(4-Metanosulfonil-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3034**),

(1-Etil-1H-pirazol-3-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3035**),

(1-Etil-1H-pirazol-4-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3036**),

[5-(5-Metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(5-trifluorometil-2H-pirazol-3-il)-amina (**P-3037**),

(5-Isopropoxi-2H-pirazol-3-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3038**),

(6-Etoxi-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amin (**P-3039**),

[2-Fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3040**),

[6-Fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-3041**),

[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-3042**),

[2-Fluoro-6-(6-metil-piridina-3-ilamino)-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3043**),

(5-Cloro-1H-pirrol[2,3-b]piridina-3-il)-[2-fluoro-6-(6-metil-piridina-3-ilamino)-piridina-3-il]-metanona (**P-3044**),

[6-(6-Etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3045**), (6-Etil-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3048**), [6-(6-Etil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3049**), (6-Ciclopropil-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3050**), [6-(6-Ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3051**), [6-(6-Ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3052**), (6-Ciclopropil-piridina-3-il)-[6-fluoro-5-(1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3053**), [6-Fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-4001**), [6-Fluoro-5-(4-metil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-4002**), (6-Cloro-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4003**), (6-Ciclopropil-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4004**), (6-Etoxi-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4005**), (6-Etoxi-piridina-3-il)-[6-fluoro-5-(4-metil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-

piridina-2-il]-amina (**P-4006**),

(6-Etil-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4007**),

(6-Etoxi-piridina-3-il)-{6-fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-amina (**P-4008**),

(6-Etil-piridina-3-il)-[6-fluoro-5-(4-metil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4009**),

[6-Fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-4010**),

(1-Etil-1H-pirazol-4-il)-[6-fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4011**),

[5-(4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(1-etil-1H-pirazol-4-il)-amina (**P-4012**),

(1-Etil-1H-pirazol-4-il)-[6-fluoro-5-(4-metil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4013**),

(1-Etil-1H-pirazol-4-il)-{6-fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-amina (**P-4014**),

{6-Fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-(6-metil-piridina-3-il)-amina (**P-4015**),

(6-Etil-piridina-3-il)-{6-fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-amina (**P-4016**),

[5-(4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-4017**),

[5-(4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-4018**),

{6-Fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-(6-metoxi-piridina-3-il)-amina (**P-4019**), (6-Bromo-piridina-3-il)-[5-(4-etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-amina (**P-4020**), [5-(4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-piridina-3-il-amina (**P-4021**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-metanona (**P-4022**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-4023**), [6-(6-Etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-il)-metanona (**P-4024**), (4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-il)-[2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-metanona (**P-4025**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-etoxi-piridina-3-il)-amina (**P-4026**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[6-(6-etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-metanona (**P-4027**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-etil-piridina-3-il)-amina (**P-4028**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[6-(6-etil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-metanona (**P-4029**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-4030**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[2-fluoro-6-(6-metil-piridina-3-

ilamino)-piridina-3-il]-metanona (**P-4031**), [6-(6-Etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-metil-7H-pirrol[2,3-d]pirimidina-5-il)-metanona (**P-4032**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(1-etil-1H-pirazol-4-il)-amina (**P-4036**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[6-(1-etil-1H-pirazol-4-ilamino)-2-fluoro-piridina-3-il]-metanona (**P-4037**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(5-metil-piridina-3-il)-amina (**P-4038**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[2-fluoro-6-(5-metil-piridina-3-ilamino)-piridina-3-il]-metanona (**P-4039**), [6-(6-Ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-metanona (**P-4040**), (6-Ciclopropil-piridina-3-il)-[5-(4-ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-amina (**P-4041**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6,7-dihidro-5H-[1]piridina-3-il)-amine (**P-4042**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[6-(6,7-dihidro-5H-[1]piridina-3-ilamino)-2-fluoro-piridina-3-il]-metanona (**P-4043**), (6-Ciclopropil-piridina-3-il)-[6-fluoro-5-(4-metil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4044**), [6-(6-Ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-metil-7H-pirrol[2,3-d]pirimidina-5-il)-metanona (**P-4045**), (4-amino-7H-pirrol[2,3-d]pirimidina-5-il)-[2-cloro-6-[(4,4-

difluorociclohexil)amino]-3-piridil]metanona (**P-4046**),
[2-cloro-6-[(4,4-difluorociclohexil)amino]-3-piridil]-[4-(2-metilprop-1-enilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4047**),
(4-amino-7H-pirrol[2,3-d]pirimidina-5-il)-[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]metanona (**P-4048**),
[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[(2-hidroxi-2-metil-propilo)amino]-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4049**),
[2-cloro-6-[(4,4-difluorociclohexil)amino]-3-piridil]-[4-(etilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4050**),
[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]-[4-(etilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4051**),
[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]-[4-(2,2,2-trifluoroetilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4052**),
[4-(ciclopropilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]metanona (**P-4053**),
[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]-[4-(metilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4054**),
[4-(tert-butilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]metanona (**P-4055**),
[4-[(4,4-difluorociclohexil)amino]-7H-pirrol[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]metanona (**P-4056**),
[2-cloro-6-[(4,4-difluorociclohexil)amino]-3-piridil]-[4-(2,2,2-trifluoroetilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4057**),
[2-cloro-6-[(4,4-difluorociclohexil)amino]-3-piridil]-[4-(metilamino)-7H-pirrol[2,3-

d]pirimidina-5-il]metanona (**P-4058**),

[2-cloro-6-[(4,4-difluorociclohexil)amino]-3-piridil]-[4-(ciclopropilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4059**),

[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-(etilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4060**),

[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-(2,2,2-trifluoroetilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4061**),

[4-(ciclopropilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]metanona (**P-4062**),

[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-(metilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4063**),

[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[(2-hidroxi-2-metil-propilo)amino]-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4064**),

(4-amino-7H-pirrol[2,3-d]pirimidina-5-il)-[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]metanona (**P-4065**),

[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]-[4-(isopropiloamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4066**),

[4-(ciclopropilmetilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]metanona (**P-4067**),

[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]-[4-(propiloamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4068**),

[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]-[4-(1-peperidil)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4069**),

[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]-(4-morfolino-7H-pirrol[2,3-

d]pirimidina-5-il)metanona (**P-4070**),

[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]-[4-[[6-(trifluorometil)-3-piridil]metilamino]-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4071**),

[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]-[4-[[(1S)-1-(4-fluorofenil)etil]amino]-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4072**),

[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]-[4-(tetrahidrofurano-2-ilmetilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4073**),

[4-[(1-etil-4-peperidil)amino]-7H-pirrol[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]metanona (**P-4074**),

[4-(ciclopentilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]metanona (**P-4075**),

[4-(ciclobutilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]metanona (**P-4076**),

[4-(1-etilpropiloamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]metanona (**P-4077**),

[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]-[4-(sec-butilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4078**),

[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]-[4-(3-metoxipropiloamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4079**),

[4-(butilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]metanona (**P-4080**),

[4-(etilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]metanona (**P-4081**),

[4-(ciclohexilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(6-metoxi-3-

piridil)amino]-3-piridil]metanona (**P-4082**),
[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]-[4-(metilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4083**),
[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]-[4-(2,2,2-trifluoroetilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4084**),
[2-metoxi-6-[(6-metoxi-3-piridil)amino]-3-piridil]-[4-(metilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4085**),
[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[(6-metil-3-piridil)amino]-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4086**),
[6-[(4,4-difluorociclohexil)amino]-3-piridil]-[4-(2,2,2-trifluoroetilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4087**),
[4-(ciclopropilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[6-[(4,4-difluorociclohexil)amino]-3-piridil]metanona (**P-4088**),
[6-[(4,4-difluorociclohexil)amino]-3-piridil]-[4-(metilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4089**),
[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-(2,2,2-trifluoroetilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4090**),
[4-(ciclopropilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[2-flúor-6-[[6-(trifluorometil)-3-piridil]amino]-3-piridil]metanona (**P-4091**),
[2-fluoro-6-[[6-(trifluorometil)-3-piridil]amino]-3-piridil]-[4-(metilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4092**),
[4-(ciclopropilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]metanona (**P-4093**),
[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-(metilamino)-7H-

pirrol[2,3-d]pirimidina-5-il]metanona (**P-4094**),
[4-(ciclobutilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]metanona (**P-4095**),
[4-[(4,4-difluorociclohexil)amino]-7H-pirrol[2,3-d]pirimidina-5-il]-[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]metanona (**P-4096**),
[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1S)-1-(4-fluorofenil)etil]amino]-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4097**),
[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]-[4-(3-metoxipropiloamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4098**),
[4-(ciclopentilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[6-[(6-etil-3-piridil)amino]-2-fluor-3-piridil]metanona (**P-4099**),
[4-(butilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]metanona (**P-4100**),
[6-(ciclohexilamino)-2-fluoro-3-piridil]-[4-(isopropiloamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4101**),
[6-(ciclohexilamino)-2-fluoro-3-piridil]-[4-(metilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4102**),
[2-fluoro-6-[(5-metoxi-3-piridil)amino]-3-piridil]-[4-(2,2,2-trifluoroetilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4103**),
[4-(ciclohexilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(5-metoxi-3-piridil)amino]-3-piridil]metanona (**P-4104**),
[2-fluoro-6-[(5-metoxi-3-piridil)amino]-3-piridil]-[4-(propiloamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4105**),
[2-fluoro-6-[(5-metoxi-3-piridil)amino]-3-piridil]-[4-(isopropiloamino)-7H-

pirrol[2,3-d]pirimidina-5-il]metanona (**P-4106),**
[4-(ciclopropilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(5-metoxi-3-piridil)amino]-3-piridil]metanona (**P-4107**),
[2-fluoro-6-[(5-metoxi-3-piridil)amino]-3-piridil]-[4-(metilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4108**),
[2-cloro-6-(ciclohexilamino)-3-piridil]-[4-(isopropiloamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4109**),
[2-cloro-6-(ciclohexilamino)-3-piridil]-[4-(metilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4110**),
[4-(ciclohexilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(6-metil-3-piridil)amino]-3-piridil]metanona (**P-4111**),
[2-fluoro-6-[(6-metil-3-piridil)amino]-3-piridil]-[4-(2,2,2-trifluoroetilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4112**),
[4-(ciclopropilmetilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(6-metil-3-piridil)amino]-3-piridil]metanona (**P-4113**),
[2-fluoro-6-[(6-metil-3-piridil)amino]-3-piridil]-[4-(propiloamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4114**),
[2-fluoro-6-[(6-metil-3-piridil)amino]-3-piridil]-[4-(metilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4115**),
[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]-[4-(tetrahidropiran-4-ilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4116**),
[6-[(6-etil-3-piridil)amino]-2-flúor-3-piridil]-[4-(isopropiloamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4117**),
[4-(ciclopropilmetilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[6-[(6-etil-3-

piridil)amino]-2-fluoro-3-piridil]metanona (**P-4118**),
[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]-[4-(2-metoxietilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4119**),
[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]-[4-(2,2,2-trifluoroetilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4120**),
[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]-[4-(isobutilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4121**),
[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]-[4-(propiloamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4122**),
[4-(etilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]metanona (**P-4123**),
[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]-[4-(metilamino)-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4124**),
[4-(ciclopropilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[6-[(6-etil-3-piridil)amino]-2-flúor-3-piridil]metanona (**P-4125**),
[4-(ciclopropilamino)-7H-pirrol[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]metanona (**P-4126**),
N-ciclopropil-5-[[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]metil]-7H-pirrol[2,3-d]pirimidina-4-amina (**P-4127**),
5-[[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]metil]-N-(2,2,2-trifluoroetil)-7H-pirrol[2,3-d]pirimidina-4-amina (**P-4128**),
N-ciclopropil-5-[[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]metil]-7H-pirrol[2,3-d]pirimidina-4-amina (**P-4129**),
5-[[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]metil]-N-(2,2,2-

trifluoroetil)-7H-pirrol[2,3-d]pirimidina-4-amina (**P-4130**),

5-[[6-(ciclohexilamino)-2-fluoro-3-piridil]metil]-N-ciclopropil-7H-pirrol[2,3-d]pirimidina-4-amina (**P-4131**),

[2-fluoro-6-[(6-metoxi-3-piridil)amino]-3-piridil]-[4-[[(1R)-1-(4-fluorofenil)etil]amino]-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4132**),

[6-[(6-etil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-1-(4-fluorofenil)etil]amino]-7H-pirrol[2,3-d]pirimidina-5-il]metanona (**P-4133**), y

[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]-[4-(metilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4134**),
[4-(etilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]metanona (**P-4135**),
[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]-[4-(isopropilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4136**),
[4-(ciclopropilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]metanona (**P-4137**),
[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]-[4-(2,2,2-trifluoroetilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4138**),
[4-[[(1R)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]metanona (**P-4139**),
[4-[[(1S)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]metanona (**P-4140**),
[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]-[4-(metoximetilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4141**),
[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]-[4-(3-metoxipropilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4142**),
[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]-[4-(tetrahidropiran-4-ilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4143**),
[4-(ciclobutilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]metanona (**P-4144**),
[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(metilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4145**),

[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(etilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4146**),
[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(propilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4147**),
[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(isopropilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4148**),
[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(2,2,2-trifluoroetilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4149**),
[4-[[(1R)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]metanona (**P-4150**),
[4-[[(1S)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]metanona (**P-4151**),
[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(metoximetilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4152**),
[6-[(3,3-15difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(tetrahidropiran-4-ilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4153**),
[4-(ciclobutilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]metanona (**P-4154**),
[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(3-metoxipropilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4155**),
[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-(3-metoxipropilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4156**),
[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-(2-metoxietilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4157**),
[4-(ciclobutilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]metanona (**P-4158**),
[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-(tetrahidropiran-4-ilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4159**),
[4-[[(1R)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]metanona (**P-4160**),
[4-[[(1S)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]metanona (**P-4161**),
[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-(etilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4162**),
[4-(ciclobutilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]metanona (**P-4163**),

[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]-[4-(metoximetilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4164**),
[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]-[4-(3-metoxipropilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona(**P-4165**),
[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]-[4-(tetrahidropiran-4-ilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4166**),
[4-[[(1R)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]metanona (**P-4167**),
[4-[[(1S)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]metanona (**P-4168**),
[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1S)-1-metilpropil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4169**),
[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[(3-hidroxi-1-metil-propil)amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4170**),
[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-1-(hidroximetil)propil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4171**),
4-[[5-[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]pirrolidina-2-ona (**P-4172**),
[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-2-hidroxi-1-metil-etil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4173**),
[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1R,3R)-3-hidroxiciclohexil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4174**),
[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1R,2R)-2-hidroxiciclopentil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4175**),
1-[3-[[5-[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]pirrolidina-1-il]etanona (**P-4176**),
(2R)-2-[[5-[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]ciclohexanona (**P-4177**),
[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[(1,1-dioxotiolan-3-il)amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4178**),
[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1R,2R)-2-hidroxiciclohexil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4179**),
[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-2-metoxi-1-metil-etil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4180**),
4-[[5-[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]piperidin-2-ona (**P-4181**),

[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-2,2,2-trifluoro-1-metil-etil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4182**),
4-[[5-[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]-1-metil-piperidin-2-ona (**P-4183**),
[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[(1,1-dioxotian-3-il)amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4184**),
1-ciclopropil-4-[[5-[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]pirrolidina-2-ona (**P-4185**),
[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1S)-1-metilpropil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4186**),
[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[(3-hidroxi-1-metil-propil)amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4187**),
[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-1-(hidroximetil)propil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4188**),
4-[[5-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]pirrolidina-2-ona (**P-4189**),
[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-2-hidroxi-1-metil-etil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4190**),
[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1R,3R)-3-hidroxiciclohexil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4191**),
[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1R,2R)-2-hidroxiciclopentil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4192**),
1-[3-[[5-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]pirrolidina-1-il]etanona (**P-4193**),
(2R)-2-[[5-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]ciclohexanona (**P-4194**),
[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[(1,1-dioxotiolan-3-il)amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4195**),
[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1R,2R)-2-hidroxiciclohexil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4196**),
[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-2-metoxi-1-metil-etil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4197**),
4-[[5-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]piperidin-2-ona (**P-4198**),
[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-2,2,2-trifluoro-1-metil-etil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4199**),

4-[[5-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]-1-metil-piperidin-2-ona (**P-4200**),
[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[(1,1-dioxotian-3-il)amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona (**P-4201**),
1-ciclopropil-4-[[5-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]pirrolidina-2-ona (**P-4202**); y

Cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0412] En una de las formas de realización de los compuestos de la Fórmula I, los compuestos se seleccionan del grupo que consiste de: [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-ciclohexil-amina (**P-3001**),
[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-ciclopentil-amina (**P-3003**),
[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4,4-difluoro-ciclohexil)-amina (**P-3004**),
[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-ciclopropil-amina (**P-3005**),
[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-cicloheptil-amina (**P-3006**),
[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-ciclobutil-amina (**P-3007**),
Ciclohexil-[6-fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3008**),
[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4-metil-ciclohexil)-amina (**P-3009**),

[5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-6-fluoro-piridina-2-il]-(4,4-difluoro-ciclohexil)-amina (**P-3013**), y cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0413] En una de las formas de realización de los compuestos de la Fórmula I, los compuestos se seleccionan del grupo que consiste de: [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4,4-difluoro-ciclohexil)-amina (**P-3004**), [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-cicloheptil-amina (**P-3006**), [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-6-fluoro-piridina-2-il]-(4,4-difluoro-ciclohexil)-amina (**P-3013**), y cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0414] En una de las formas de realización de los compuestos de la Fórmula I, los se seleccionan del grupo que consiste de: (1-Etil-1H-pirazol-3-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3035**), (1-Etil-1H-pirazol-4-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3036**), (1-Etil-1H-pirazol-4-il)-[6-fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amine (**P-4011**), [5-(4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(1-etil-1H-pirazol-4-il)-amina (**P-4012**), (1-Etil-1H-pirazol-4-il)-[6-fluoro-5-(4-metil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-

piridina-2-il]-amina (**P-4013**), (1-Etil-1H-pirazol-4-il)-{6-fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-amina (**P-4014**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(1-etil-1H-pirazol-4-il)-amina (**P-4036**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[6-(1-etil-1H-pirazol-4-ilamino)-2-fluoro-piridina-3-il]-metanona (**P-4037**), y cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0415] En una de las formas de realización de los compuestos de la Fórmula I, los compuestos se seleccionan del grupo que consiste de: (4-Fluoro-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3010**), (4-Cloro-fenil)-[5-(5-cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3011**), [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4-fluoro-fenil)-amina (**P-3012**), [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(2-fluoro-fenil)-amina (**P-3014**), (2-Cloro-fenil)-[5-(5-cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3015**), [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(2-metoxi-fenil)-amina (**P-3016**), [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(3-fluoro-fenil)-amina (**P-3017**),

(4-Metoxi-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3021**), (4-Fluoro-3-metoxi-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3022**), (3-Fluoro-4-metoxi-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3023**), [5-(5-Metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4-propoxi-fenil)-amina (**P-3024**), (4-Etil-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3025**), (4-Etoxi-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3026**), (4-tert-butil-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3030**), 1,1,1,3,3,3-Hexafluoro-2-{4-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-ilamino]-fenil}-propan-2-ol (**P-3031**), [5-(5-Metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4-metilsulfonil-fenil)-amina (**P-3033**), (4-Metanosulfonil-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3034**), y cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0416] En una de las formas de realización de los compuestos de la Fórmula I, los compuestos se seleccionan del grupo que consiste de: (4-Fluoro-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-

amina (**P-3010**), (4-Cloro-fenil)-[5-(5-cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3011**), [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4-fluoro-fenil)-amina (**P-3012**), [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(2-fluoro-fenil)-amina (**P-3014**), (4-Metoxi-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3021**), (4-Etil-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3025**), (4-Etoxi-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3026**), (4-tert-butil-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3030**), 1,1,1,3,3,3-Hexafluoro-2-{4-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-ilamino]-fenil}-propan-2-ol (**P-3031**), [5-(5-Metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4-metilsulfonil-fenil)-amina (**P-3033**), y cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0417] En una de las formas de realización de los compuestos de la Fórmula I, los compuestos se seleccionan del grupo que consiste de: [5-(5-Metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(6-trifluorometil-piridina-3-il)-amina (**P-3018**),

[6-Fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-3019**),

(6-Metoxi-piridina-3-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3020**),

(6-Etoxi-piridina-3-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3027**),

(6-Etoxi-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3039**),

[2-Fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3040**),

[6-(6-Etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3045**),

[6-Fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-4001**),

[6-Fluoro-5-(4-metil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-4002**),

(6-Etoxi-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4005**),

(6-Etoxi-piridina-3-il)-[6-fluoro-5-(4-metil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4006**),

(6-Etoxi-piridina-3-il)-{6-fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-amina (**P-4008**),

[5-(4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-4018**),

{6-Fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-

il}-(6-metoxi-piridina-3-il)-amina (**P-4019**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-metanona (**P-4022**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-4023**), [6-(6-Etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-il)-metanona (**P-4024**), (4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-il)-[2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-metanona (**P-4025**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-etoxi-piridina-3-il)-amina (**P-4026**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[6-(6-etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-metanona (**P-4027**), [6-(6-Etoxi-piridina-3-ilamino)-2-fluoroor-piridina-3-il]-(4-metil-7H-pirrol[2,3-d]pirimidina-5-il)-metanona (**P-4032**), y cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0418] En una de las formas de realización de los compuestos de la Fórmula I, los compuestos se seleccionan del grupo que consiste de: [5-(5-Metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(6-trifluorometil-piridina-3-il)-amina (**P-3018**), [6-Fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-3019**), (6-Metoxi-piridina-3-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3020**),

(6-Etoxi-piridina-3-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3027**),

(6-Etoxi-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3039**),

[2-Fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3040**),

[6-(6-Etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3045**),

[6-Fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-4001**),

(6-Etoxi-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4005**),

(6-Etoxi-piridina-3-il)-[6-fluoro-5-(4-metil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4006**),

(6-Etoxi-piridina-3-il)-{6-fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-amina (**P-4008**),

[5-(4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-4018**),

{6-Fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-(6-metoxi-piridina-3-il)-amina (**P-4019**),

(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-metanona (**P-4022**),

[5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluor-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-4023**),

[5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-

etoxi-piridina-3-il)-amina (**P-4026**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[6-(6-etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-metanona (**P-4027**), [6-(6-Etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-metil-7H-pirrol[2,3-d]pirimidina-5-il)-metanona (**P-4032**), y cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0419] En una de las formas de realización de los compuestos de la Fórmula I, los compuestos se seleccionan del grupo que consiste de: [6-Fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-3041**), [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-3042**), [2-Fluoro-6-(6-metil-piridina-3-ilamino)-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3043**), (5-Cloro-1H-pirrol[2,3-b]piridina-3-il)-[2-fluoro-6-(6-metil-piridina-3-ilamino)-piridina-3-il]-metanona (**P-3044**), (6-Etil-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3048**), [6-(6-Etil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3049**), (6-Ciclopropil-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3050**), [6-(6-Ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3051**),

[6-(6-Ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3052**), (6-Ciclopropil-piridina-3-il)-[6-fluoro-5-(1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3053**), (6-Ciclopropil-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4004**), (6-Etil-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4007**), (6-Etil-piridina-3-il)-[6-fluoro-5-(4-metil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4009**), [6-Fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-4010**), {6-Fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-(6-metil-piridina-3-il)-amina (**P-4015**), (6-Etil-piridina-3-il)-{6-fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-amina (**P-4016**), [5-(4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-4017**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-etil-piridina-3-il)-amina (**P-4028**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[6-(6-etil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-metanona (**P-4029**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-4030**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[2-fluoro-6-(6-metil-piridina-3-

ilamino)-piridina-3-il]-metanona (**P-4031**), [6-(6-Ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-metanona (**P-4040**), (6-Ciclopropil-piridina-3-il)-[5-(4-ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-amina (**P-4041**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6,7-dihidro-5H-[1]piridina-3-il)-amina (**P-4042**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[6-(6,7-dihidro-5H-[1]piridina-3-ilamino)-2-fluoro-piridina-3-il]-metanona (**P-4043**), (6-Ciclopropil-piridina-3-il)-[6-fluoro-5-(4-metil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4044**), [6-(6-Ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-metil-7H-pirrol[2,3-d]pirimidina-5-il)-metanona (**P-4045**), y cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0420] En una de las formas de realización de los compuestos de la Fórmula I, los compuestos se seleccionan del grupo que consiste de: [6-Fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-3041**), [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-3042**), [2-Fluoro-6-(6-metil-piridina-3-ilamino)-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3043**), (5-Cloro-1H-pirrol[2,3-b]piridina-3-il)-[2-fluoro-6-(6-metil-piridina-3-ilamino)-piridina-3-il]-metanona (**P-3044**),

(6-Etil-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3048**), [6-(6-Etil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3049**), (6-Ciclopropil-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3050**), [6-(6-Ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3051**), [6-(6-Ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3052**), (6-Ciclopropil-piridina-3-il)-[6-fluoro-5-(1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3053**), (6-Ciclopropil-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4004**), (6-Etil-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4007**), (6-Etil-piridina-3-il)-[6-fluoro-5-(4-metil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4009**), [6-Fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-4010**), (6-Etil-piridina-3-il)-{6-fluor-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-amina (**P-4016**), [5-(4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-4017**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-

etil-piridina-3-il)-amina (**P-4028**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[6-(6-etil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-metanona (**P-4029**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-4030**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[2-fluoro-6-(6-metil-piridina-3-ilamino)-piridina-3-il]-metanona (**P-4031**), [6-(6-Ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-metanona (**P-4040**), (6-Ciclopropil-piridina-3-il)-[5-(4-ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-amina (**P-4041**), y cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0421] En una de las formas de realización de los compuestos de la Fórmula I, los compuestos se seleccionan del grupo que consiste de: (6-Cloro-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4003**), (6-Bromo-piridina-3-il)-[5-(4-etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-amina (**P-4020**), [5-(4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-piridina-3-il-amina (**P-4021**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(5-metil-piridina-3-il)-amina (**P-4038**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[2-fluoro-6-(5-metil-piridina-3-ilamino)-piridina-3-il]-metanona (**P-4039**), y

cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0422] En una de las formas de realización de los compuestos de la Fórmula I, los compuestos se seleccionan del grupo que consiste de: [6-Fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-3019**), (6-Metoxi-piridina-3-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3020**), (4-Metoxi-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3021**), [2-Fluoro-6-(6-metil-piridina-3-ilamino)-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3043**), (5-Cloro-1H-pirrol[2,3-b]piridina-3-il)-[2-fluoro-6-(6-metil-piridina-3-ilamino)-piridina-3-il]-metanona (**P-3044**), [6-(6-Etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3045**), (6-Etil-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3048**), [6-(6-Etil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3049**), (6-Etoxi-piridina-3-il)-{6-fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-amina (**P-4008**), (6-Etil-piridina-3-il)-[6-fluoro-5-(4-metil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4009**), (6-Etil-piridina-3-il)-{6-fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-

ilmetil]-piridina-2-il}-amina (**P-4016**), [5-(4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-4018**), {6-Fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-(6-metoxi-piridina-3-il)-amina (**P-4019**), (6-Bromo-piridina-3-il)-[5-(4-etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-amina (**P-4020**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-4023**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-etoxi-piridina-3-il)-amina (**P-4026**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-etil-piridina-3-il)-amina (**P-4028**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[6-(6-etil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-metanona (**P-4029**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-4030**), y cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0423] En una de las formas de realización de los compuestos de la Fórmula I, los compuestos se seleccionan del grupo que consiste de: [6-Fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-3019**), (6-Metoxi-piridina-3-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3020**),

(4-Metoxi-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3021**), (6-Etil-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3048**), (6-Etil-piridina-3-il)-[6-fluoro-5-(4-metil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4009**), (6-Etil-piridina-3-il)-{6-fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-amina (**P-4016**), [5-(4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-4018**), (6-Bromo-piridina-3-il)-[5-(4-etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-amina (**P-4020**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-etoxi-piridina-3-il)-amina (**P-4026**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-floro-piridina-2-il]-(6-etil-piridina-3-il)-amina (**P-4028**), (4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-il)-[6-(6-etil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-metanona (**P-4029**), y cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0424] En una de las formas de realización de los compuestos de la Fórmula I, los compuestos se seleccionan del grupo que consiste de: [2-Fluoro-6-(6-metil-piridina-3-ilamino)-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3043**), (5-Cloro-1H-pirrol[2,3-b]piridina-3-il)-[2-fluoro-6-(6-metil-piridina-3-ilamino)-

piridina-3-il]-metanona (**P-3044**), [6-(6-Etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3045**), [6-(6-Etil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrol[2,3-b]piridina-3-il)-metanona (**P-3049**), (6-Etoxi-piridina-3-il)-{6-fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-amina (**P-4008**), {6-Fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-(6-metoxi-piridina-3-il)-amina (**P-4019**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-amina (**P-4023**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-4030**), y cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0425] En una de las formas de realización de los compuestos de la Fórmula I, los compuestos se seleccionan del grupo que consiste de: [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4,4-difluoro-ciclohexil)-amina (**P-3004**), [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-6-fluoro-piridina-2-il]-(4,4-difluoro-ciclohexil)-amina (**P-3013**), [6-Fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-3041**), [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-3042**),

[6-Fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-4010**), (1-Etil-1H-pirazol-4-il)-[6-fluoro-5-(4-metoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4011**), [5-(4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(1-etil-1H-pirazol-4-il)-amina (**P-4012**), (1-Etil-1H-pirazol-4-il)-[6-fluoro-5-(4-metil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amina (**P-4013**), [5-(4-Ciclopropil-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(1-etil-1H-pirazol-4-il)-amina (**P-4036**), y cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0426] En una de las formas de realización de los compuestos de la Fórmula I, los compuestos se seleccionan del grupo que consiste de: [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-cicloheptil-amina (**P-3006**), (4-Fluoro-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3010**), (4-Cloro-fenil)-[5-(5-cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3011**), [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4-fluoro-fenil)-amina (**P-3012**), [5-(5-Cloro-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(2-fluoro-fenil)-amina (**P-3014**), [5-(5-Metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(6-trifluorometil-

piridina-3-il)-amina (**P-3018**), (4-Etoxi-fenil)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3026**), (6-Etoxi-piridina-3-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3027**), (1-Etil-1H-pirazol-4-il)-[5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amina (**P-3036**), (6-Etoxi-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrol[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amina (**P-3039**), (1-Etil-1H-pirazol-4-il)-{6-fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrol[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-amina (**P-4014**), [5-(4-Etoxi-7H-pirrol[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amina (**P-4017**), y cualquier sal, profármaco, solvato, tautómero o estereoisómero del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

En algunas formas de realización, la invención provee uno de los compuestos descritos en la Tabla 7 y cualquier sal, solvato, profármaco, estereoisómero o tautómeros del mismo. En algunas formas de realización, la sal es una sal farmacéuticamente aceptable.

[0427] En referencia a los compuestos aquí descritos, a menos que se indique claramente lo contrario, la especificación de un compuesto o grupo de compuestos incluye sales de dichos compuestos (incluyendo sales farmacéuticamente aceptables), fórmulas de dichos compuestos (incluyendo fórmulas farmacéuticamente aceptables), conjugados del mismo, derivados, formas, profármacos y todos los isómeros del mismo. En referencia a la composición, kits, métodos de uso, etc., de los compuestos de la Fórmula I como se describe aquí, se

entiende (a menos que se indique lo contrario) que un compuesto de la Fórmula I incluye todas las sub-formas de realización del mismo (incluyendo cualquier Fórmula subgenérica Ia la Iae).

[0428] En un quincuagésimo-sexto aspecto, un compuesto de la Fórmula I es un inhibidor de quinasa Fms y tiene un CI_{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 determinado en un ensayo de actividad de quinasa Fms generalmente aceptado. En algunas formas de realización, el compuesto es selectivo relativo a otras proteínas quinasas, tales como el cociente de CI_{50} por otra quinasa comparablemente evaluada, dividida por el CI_{50} por quinasa Fms es >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, donde la otra proteína quinasa incluye, pero no está limitada a CSK, Quinasa Receptora de Insulina, AMPK, PDGFR o VEGFR. En algunas formas de realización, el compuesto es selectivo relativo a la proteína quinasa Kit, tales como el cociente de CI_{50} por quinasa Kit comparablemente evaluada, dividida por el CI_{50} por quinasa Fms es >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100.

[0429] In quincuagésimo-séptimo aspecto, un compuesto de la Fórmula I es un inhibidor selectivo Fms, es decir, se inhibirá selectivamente la quinasa Fms relativa a quinasa Kit. En algunas formas de realización el compuesto tendrá un CI_{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 según lo determinado en el ensayo de actividad de quinasa Kit generalmente aceptado y cuando el ensayo de actividad de quinasa Kit generalmente aceptado tendrá un cociente de CI_{50} por quinasa Kit dividida por el CI_{50} por kinasa Fms de >20, también >30, también >40, también >50,

también >60, también >70, también >80, también >90, también >100. En algunas formas de realización, el compuesto también es selectivo con relación a proteínas quinasas distintas a la Kit, tales como el cociente de CI_{50} por otra quinasa comparablemente evaluada, dividida por el CI_{50} por quinasa Fms es >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, donde la otra proteína quinasa incluye, pero no está limitada a Flt-3, CSK, Quinasa Receptora de Insulina, AMPK, PDGFR o VEGFR. En una de las formas de realización, el inhibidor selectivo de la Fms no cruza de forma efectiva la barrera sangre-cerebro. En una de las formas de realización, el inhibidor selectivo de la Fms cruza de forma efectiva la barrera sangre-cerebro.

[0430] En un quincuagésimo-octavo aspecto, un compuesto de la Fórmula I es un inhibidor dual de las quinasas Fms/Kit, es decir, será aproximadamente equipotente con respecto a la inhibición de la quinasa Fms y la quinasa Kit. En algunas formas de realización el compuesto tendrá un CI_{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 como se determina en el ensayo de actividad de quinasa Fms generalmente aceptado y tendrá un CI_{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 como se termina en el ensayo de actividad de quinasa Kit generalmente aceptado, donde el cociente de CI_{50} por quinasa Kit dividido por el CI_{50} por quinasa Fms en el rango de 20 a 0.05, también 10 a 0.1, también 5 a 0.2. En algunas formas de realización, el compuesto es selectivo relativo a otras proteínas quinasas, tales como el cociente de CI_{50} por otra quinasa comparablemente evaluada, dividida por el CI_{50} por quinasa Fms (y/o quinasa Kit) es >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, donde la otra proteína

quinsasa incluye, pero no está limitada a CSK, Quinasa Receptora de Insulina, AMPK, PDGFR o VEGFR.

[0431] En un quincuagésimo-noveno aspecto, un compuesto de la Fórmula I es un inhibidor dual de las quinasas Fms/Flt-3, es decir, será aproximadamente equipotente con respecto a la inhibición de la quinasa Flt-3. En algunas formas de realización los compuestos tendrán un CI_{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 como se determina en el ensayo de actividad de quinasa Fms generalmente aceptado y tendrá un CI_{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 como se determina en el ensayo de actividad de quinasa Flt-3 generalmente aceptado, donde el cociente de CI_{50} por quinasa Flt-3 dividida por el CI_{50} por quinasa Fms está en el rango de 20 a 0.05, también 10 a 0.1, también 5 a 0.2. En algunas formas de realización, el compuesto es selectivo relativo a otras proteínas quinasas, tales como el cociente de CI_{50} por otra quinasa comparablemente evaluada, dividida por el CI_{50} por quinasa Fms (y/o quinasa Flt3) es >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, donde la otra proteína quinasa incluye, pero no está limitada a CSK, Quinasa Receptora de Insulina, AMPK, PDGFR o VEGFR. En algunas formas de realización, inhibidor dual Fms/Flt-3 es selectivo con respecto a Kit. En algunas formas de realización, el inhibidor dual Fms/Flt-3 también inhibe a Kit.

[0432] En un sexagésimo aspecto, un compuesto de la Fórmula I es un inhibidor dual de las quinsasas Fms/Trk, es decir, será aproximadamente equipotente con respecto a la inhibición de la quinasa Fms y la quinasa Trk. En algunas formas de realización los compuestos tendrán un CI_{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 como se determina en el ensayo de actividad de quinasa Fms generalmente aceptado y tendrá un CI_{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 como se determina en el ensayo de actividad de quinasa Trk generalmente aceptado (incluyendo una o más de TrkA, TrkB, y TrkC), donde el cociente de CI_{50} por quinasa Trk (al menos una de las TrkA, TrkB, y TrkC) dividida por el CI_{50} por quinasa Fms está en el rango de 20 a 0.05, también 10 a 0.1, también 5 a 0.2. En algunas formas de realización, el compuesto es selectivo relativo a otras proteínas quinasas, tales como el cociente de CI_{50} por otra quinasa comparablemente evaluada, dividida por el CI_{50} por quinasa Fms (y/o quinasa Trk) es >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, donde la otra proteína quinasa incluye, pero no está limitada a CSK, Quinasa Receptora de Insulina, AMPK, PDGFR o VEGFR. En algunas formas de realización, el inhibidor dual de las quinasas Fms/Trk es selectivo con respecto a Kit. En algunas formas de realización, el inhibidor dual Fms/Trk también inhibe a Kit.

[0433] Adicionalmente a cualquier aspecto y forma de realización anteriormente mencionadas, un compuesto de la Fórmula I también inhibirá los efectos de mutación de la quinasa, incluyendo, pero no limitada a, mutación que se relaciona con el estado de la enfermedad, tal como un cáncer.

[0434] En un sexagésimo-primero aspecto, las composiciones se suministran de tal forma que incluyan una cantidad terapéuticamente efectiva de cualquier más compuestos como de la Fórmula I y al menos un portador excipiente, y/o diluyent, farmacéuticamente aceptable, incluyendo combinaciones de dos o más compuestos

de la Fórmula I. La composición también puede incluir una pluralidad de distintos compuestos farmacológicamente activos, que pueden incluir una pluralidad de compuestos de la Fórmula I. En ciertas formas de realización, la composición puede incluir uno o más compuestos de la Fórmula I junto con uno o más compuestos que sean terapéuticamente efectivos para la misma indicación de enfermedad. En un primer aspector, la composición incluye uno o más compuestos de la Fórmula I junto con uno o más compuestos que sean terapéuticamente efectivos para la misma indicación de la enfermedad, donde los compuestos tengan un efecto sinérgico en la indicación de la enfermedad. En una de las formas de realización, la composición incluye uno o más compuestos de la Fórmula I efectivos al tratar cáncer y uno o más de otros compuestos que sean efectivos al tratar el mismo cáncer, además donde los compuestos sean sinérgicamente efectivos al tratar el cáncer.

[0435] En un sexagésimo-segundo aspecto, se suministran métodos para tratar una enfermedad o condición mediada por una o más proteína quinasa Fms, proteína quinasa Kit, proteína quinasa Flt3 y proteína quinasa Trk en un sujeto con necesidad de éstos, donde el método involucra administrar al sujeto una cantidad efectiva de uno o más compuestos de los compuestos de la Fórmula I o una composición o una composición consiste de uno o más compuestos de la Fórmula I. En ciertas formas de realización, el método involucra administrar al sujeto una cantidad efectiva de un compuesto de la Fórmula I o una composición consiste de un compuesto de la Fórmula I en combinación con una o más terapias para tratar la enfermedad o condición.

[0436] En un sexagésimo-tercero aspecto, se suministran los métodos para tratar una enfermedad o condición mediada por la proteína quinasa Fms en un sujeto de necesidad de éstos, donde el método involucra administrar al sujeto una cantidad

efectiva de uno o más compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I. En ciertas formas de realización el mpetodo involucra administrar al sujeto una cantidad efectiva de un compuesto de la Fórmula I o una composición consiste de un compuesto de la Fórmula I en combinación con una o más terapias para tratar la enfermedad o condición.

[0437] En un sexagésimo-cuarto aspecto, se suministran métodos para tratar una enfermedad o condición mediada por proteína quinasa Trk en un sujeto de necesidad de éstos, donde el método involucra administrar al sujeto una cantidad efectiva de uno o más compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I. En ciertas formas de realización el método involucra administrar al sujeto una cantidad efectiva de un compuesto de la Fórmula I o una composición consiste de un compuesto de la Fórmula I en combinación con una o más terapias apropiadas para tratar la enfermedad o condición.

[0438] En un sexagésimo-quinto aspecto, se suministran métodos para tratar una enfermedad o condición mediada por proteína quinasa Kit En un sujeto de necesidad de éstos, donde el método involucra administrar al sujeto una cantidad efectiva de uno o más compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I. En ciertas formas de realización el método involucra administrar al sujeto una cantidad efectiva de un compuesto de la Fórmula I o una composición consiste de un compuesto de la Fórmula I en combinación con una o más terapias apropiadas para tratar la enfermedad o condición.

[0439] En un sexagésimo-sexto aspecto, se suministran métodos para tratar una enfermedad o condición mediada por proteína quinasa Flt3 en un sujeto de necesidad de éstos, donde el método involucra administrar al sujeto una cantidad efectiva de uno o más compuestos de la Fórmula I o una composición consiste de

uno o más compuestos de la Fórmula I. En ciertas formas de realización el método involucra administrar al sujeto una cantidad efectiva de un compuesto de la Fórmula I o una composición consiste de un compuesto de la Fórmula I en combinación con una o más terapias apropiadas para tratar la enfermedad o condición.

[0440] En un sexagésimo-séptimo aspecto, se suministran métodos para tratar una enfermedad o condición mediada por proteína quinasa Fms y proteína quinasa Kit en un sujeto de necesidad de éstos, donde el método involucra administrar al sujeto una cantidad efectiva de uno o más inhibidores duales Fms/Kit de la Fórmula I o una composición consiste de uno o más inhibidores duales Fms/Kit de la Fórmula I. En ciertas formas de realización el método involucra administrar al sujeto una cantidad efectiva de un inhibidor dual Fms/Kit de la Fórmula I o una composición consiste de un inhibidor dual Fms/Kit de la Fórmula I en combinación con una o más terapias apropiadas para tratar la enfermedad o condición.

[0441] En un sexagésimo-octavo aspecto, se suministran métodos para tratar una enfermedad o condición mediada por proteína quinasa Fms y proteína quinasa Flt-3 en un sujeto de necesidad de éstos, donde el método involucra administrar al sujeto una cantidad efectiva de uno o más inhibidores duales Fms/Flt-3 de la Fórmula I o una composición consiste de uno o más inhibidores duales Fms/Flt-3 de la Fórmula I. En ciertas formas de realización el método involucra administrar al sujeto una cantidad efectiva de un inhibidor dual Fms/Flt-3 de la Fórmula I o una composición consiste de un inhibidor dual Fms/Flt-3 de la Fórmula I en combinación con una o más terapias apropiadas para tratar la enfermedad o condición.

[0442] En un sexagésimo-noveno aspecto, se suministran métodos para tratar una enfermedad o condición mediada por proteína quinasa Fms y proteína quinasa Trk en un sujeto de necesidad de éstos, donde el método involucra administrar al sujeto

una cantidad efectiva de uno o más inhibidores duales Fms/Trk de la Fórmula I o una composición consiste de uno o más inhibidores duales Fms/Trk de la Fórmula I. En ciertas formas de realización el método involucra administrar al sujeto una cantidad efectiva de un inhibidor dual Fms/Trk de la Fórmula I o una composición consiste de un inhibidor dual Fms/Trk de la Fórmula I en combinación con una o más terapias apropiadas para tratar la enfermedad o condición.

[0443] En un septuagésimo aspecto, la invención suministra un método para tratar un cáncer en un sujeto con necesidad de éste al administrar al sujeto una cantidad efectiva de uno o más compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I, en combinación con una o más terapias o procedimientos médicos efectivos al tratar cáncer. Otras terapias o procedimientos médicos incluyen terapias anticáncer apropiadas (por ejemplo terapia con droga, terapia con vacunas, terapias genéticas, terapia fotodinámica) o procedimientos médicos (por ejemplo cirugía, tratamiento con radiación, calentamiento hipertermia, trasplante de médula ósea o células madres). En una de las formas de realización, se seleccionan una o más terapias anticáncer apropiadas o procedimientos médicos para el tratamiento con un agente quimioterapéutico (por ejemplo medicamente quimioterapéutico), tratamiento por radiación (por ejemplo rayos-x, rayo-□ o haz de partículas de electrón, protón, neutrón □), calentamiento hipertermia (por ejemplo ablación por microonda, ultrasonido, radiofrecuencia), terapia con vacunas (por ejemplo vacuna del gen AFP carcinoma hpatocelular, vacuna de vector adenoviral AFP, AG-858, secreción de GM-CSF- alogénicas, vacuna de cáncer de seno, vacunas con células péptido dendríticas), terapia genética (por ejemplo vector Ad5CMV-p53, adenovector que codifica MDA7, adenovirus 5 del factor alfa en

necrosis tumoral), terapia fotodinámica (por ejemplo ácido aminolevulínico, motexafina lutecio), cirugía o trasplante de médula ósea y células madres.

[0444] En un septuagésimo-primero aspecto, la invención suministra un método para tratar un cáncer en un sujeto con necesidad de éste al administrar al sujeto una cantidad efectiva de uno o más compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I, en combinación con uno o más agentes quimioterapéuticos apropiados. En una de las formas de realización, se seleccionan uno o más agentes quimioterapéuticos apropiados de un agente alquilante, incluyendo, pero no limitados a, adozelesin, altretamina, bendamustina, bizelesin, busulfán, carboplatino, carboquona, carmofur, carmustina, clorambucil, cisplatino, ciclofosfamida, dacarbazina, estramustina, etoglucida, fotemustina, hepsulfam, ifosfamida, improsulfan, irofulveno, lomustina, mannosulfan, mecloretamina, melfalán, mitobronitol, nedaplatino, nimustina, oxaliplatino, piposulfan, prednimustine, procarbazina, ranimustina, satraplatino, semustina, estreptozocina, temozolomida, tiotepa, treosulfan, triazicuona, trietilenomelamina, triplatino tetranitrato, trofosfamida y uramustina; un antibiótico, incluyendo, pero no limitados a aclarubicina, amrubicina, bleomicina, dactinomicina, daunorubicina, doxorubicina, elsamitrucina, epirubicina, idarubicina, menogarilo, mitomicina, neocarzinostatina, pentostatina, pirarubicina, plicamicina, valrubicina y zorubicina; un antimetabolito, incluyendo, pero no limitados a aminopterina, azacitidina, azatioprina, capecitabina, cladribina, clofarabina, citarabina, decitabina, floxuridina, fludarabina, 5-fluorouracilo, 2'-F-ara-deoxiuridina, gemcitabina, hidroxiurea, mercaptopurina, metotrexato, nelarabina, pemetrexed, pralatrexato, azatioprina, raltitrexed, tegafur-uracilo, tioguanina, trimetoprim, trimetrexato y vidarabina; una inmunoterapia, incluendo, pero no limitadas a alemtuzumab, bevacizumab,

cetuximab, denileukin diftitox, galiximab, gemtuzumab, ofatumumab, panitumumab, pertuzumab, rituximab, tositumomab, trastuzumab y 90 Y ibritumomab tiuxetan, ipilimumab y tremelimumab; una hormona u hormona antagonista, incluyendo, pero no limitadas a anastrozola, andrógenos, bicalutamida, buserelina, Degarelix, dietilstilbestrol, exemestano, flutamida, fulvestrant, goserelin, idoxifeno, letrozole, leuprolide, megestrol, nilutamida, raloxifene, tamoxifen, 4-hidroxitamoxifen, toremifene y triptorelin; un taxano, incluyendo, pero no limitadas a DJ-927, docetaxel, TPI 287, larotaxel, ortataxel, paclitaxel, DHA-paclitaxel y tesetaxel; un retinoide, incluyendo, pero no limitados a alitretinoína, bexaroteno, fenretinida, isotretinoína y tretinoína; un alcaloide, incluyendo, pero no limitados a demecolcina, homoharringtonina, vinblastina, vincristina, vindesina, vinflunina y vinorelbina; un agente antiangiogénico, incluyendo, pero no limitados a AE-941 (GW786034, Neovastat), ABT-510, 2-metoxiestradiol, lenalidomida y talidomida; un inhibidor topoisomerasa, incluyendo, pero no limitados a amsacrina, belotecan, edotecarina, etopósido, fosfato de etopósido, exatecan, irinotecan (también metabolito activo SN-38 (7-etil-10-hidroxi-camptotecina)), lucantona, mitoxantrona, pixantrona, rubitecan, teniposida, topotecan y 9-aminocamptotecina; un inhibidor de quinasa, incluyendo, pero no limitadas a axitinib (AG 013736), dasatinib (BMS 354825), erlotinib, gefitinib, flavopiridol, imatinib mesilato, lapatinib, motesanib difosfato (AMG 706), nilotinib (AMN107), pazopanib, seliciclib, sorafenib, sunitinib malato, AEE-788, BMS-599626, UCN-01 (7-hidroxistaurosporina), PLX4032, vatalanib, inhibidores mTOR (por ejemplo temsirolimus, everolimus, deforolimus, rapamicina), inhibidores PI3K (por ejemplo BEZ235, GDC-0941, XL147, XL765, CAL-101, PX-866, BGT226, GSK1059615), inhibidores Cdk4 (por ejemplo PD-332991, AG-024322), inhibidores Akt (por

ejemplo GSK2110183, SR13668), inhibidores MEK (por ejemplo PD0325901, AZD8330, GSK1120212, RO4987655, RDEA119, XL518); un inhibidor de transducción de señal focalizado, incluyendo, pero no limitado a bortezomib y geldanamicina; un modificador de respuesta biológica, incluyendo, pero no limitado a imiquimod, interferon-□ e interleukin-2; y otros quimioterapéuticos, incluyendo, pero no limitados a 3-AP (3-amino-2-carboxialdehido tiosemicarbazona), altrasentan, aminoglutetiimida, anagrelida, asparaginasa, briostatina-1, cilengitida, elesclomol, mesilato de eribulina (E7389), ixabepilona, lonidamina, masoprocol, mitoguanazona, oblimersen, sulindac, testolactona, tiazofurín, inhibidores COX-2 (por ejemplo celecoxib, rofecoxib, valdecoxib, lumiracoxib, etoricoxib), inhibidores Hsp90 (por ejemplo tanespimicina) e inhibidores farnesiltransferasa inhibitors (por ejemplo tipifarnib).

[0445] En un septuagésimo-segundo aspecto, la invención suministra kits que incluyen uno o más compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I. En algunas formas de realización, el compuesto o composición está empacado, es decir, en un frasco ampolla, botella, frasco que puede ser empacado adicionalmente, por ejemplo, dentro de una caja, sobre o bolsael compuesto o composición está aprobado por la Administración de Alimentos y Medicamentos de Estados Unidos o una agencia regulatoria similar para la administración a mamíferos, por ejemplo un humano; el compuesto o composición está aprobado para la administración de mamíferos, por ejemplo un humano, para una enfermedad o condición mediada por proteína quinasa; el kit de invención puede incluir instrucciones para uso y/u otra indicación de que el compuesto o composición es apropiado o aprobado para la administración a mamíferos, por ejemplo un humano, para una enfermedad o condición mediada por proteína

quinasa; y el compuesto o composición puede estar empacado en dosis unitaria o en forma de dosis única, por ejemplo, píldora de dosis única, cápsulas o similares.

[0446] En los aspectos y formas de realización que involucran el tratamiento o profilaxis de una enfermedad o condición con uno o más de los compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I, la invención suministra los métodos para trata una enfermedad o condición mediada por Kit en un sujeto con necesidad de éste (por ejemplo un mamífero tal como un humano, otros primates, animales de deporte, animales de interés comercial tales como ganado, animales de finca tales como caballos o mascotas tales como perros y gatos), por ejemplo una enfermedad o condición caracterizada por actividad Kit anormal (por ejemplo actividad de quinasa). En algunas formas de realización los métodos de la invención pueden involucrar la administración al sujeto que sufre de una enfermedad o condición o está en riesgo de dicha enfermedad mediada por Kit una cantidad efectiva de uno o más compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I. En una de las formas de realización, la enfermedad mediada por Kit se selecciona del grupo que consiste de enfermedades malignas, incluyendo, pero no limitadas a mastocitoma, cáncer de pulmón microcítico, cáncer de pulmón no microcítico (NSCLC), cáncer testicular, cáncer de páncreas, cáncer de seno, cáncer de próstata, carcinoma de células de merkel, carcinoma del tracto genital femenino, sarcoma de origen neuroectodermal, carcinoma colorectal, carcinoma in situ, tumores estromales gastrointestinales (GISTs), mieloma múltiple, angiogénesis tumoral, metástasis cerebral, glioblastoma, astrocitoma, neuroblastoma, neurofibromatosis (incluyendo Neoplasia de células Schwann asociada con neurofibromatosis), leucemia mieloide aguda, leucemia linfocítica aguda, leucemia mieloide crónica, mastocitosis, melanoma y mastocitoma

en perros; enfermedades cardiovasculares, incluyendo pero no limitadas a arterioesclerosis, cardiomiopatia, falla del corazón, hipertensión arterial pulmonar y fibrosis pulmonar; indicaciones inflamatorias y autoinmunes, incluyendo, pero no limitadas a alergia, anafilaxis, asma, artritis reumatoide, rinitis alérgica, esclerosis múltiple, enfermedad intestinal inflamatoria, rechazo de trasplante, hipereosinofilia, urticaria y dermatitis; indicaciones gastrointestinales, incluyendo pero no limitadas a enfermedad por reflujo gastroesofágico (ERGE), esofagitis y úlceras en el tracto gastrointestinal; indicaciones oftalmológicas, incluyendo pero no limitadas a uveitis y Retinitis; e indicaciones neurológicas, incluyendo pero no limitadas a migraña.

[0447] En los aspectos y formas de realización que involucran el tratamiento o profilaxis de una enfermedad o condición con uno o más de los compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I, la invención suministra los métodos para tratar una enfermedad o condición mediada por Fms en un sujeto con necesidad de éste (por ejemplo un mamífero tal como un humano, otros primates, animales de deportes, animales de interés comercial tales como ganado, animales de finca tales como caballos o mascotas tales como perros y gatos), por ejemplo, una enfermedad o condición caracterizada por actividad Fms anormal (por ejemplo actividad de quinasa). En algunas formas de realización, los métodos de la invención pueden involucrar la administración al sujeto que sufre de una enfermedad o condición mediada por Fms una cantidad efectiva de uno o más compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I. En una de las formas de realización, la enfermedad mediada por Fms se selecciona del grupo que consiste de indicaciones inflamatorias y autoinmunes, incluyendo, pero no limitadas a artritis reumatoide, osteoartritis, artritis psoriásica, psoriasis, dermatitis, espondilitis anquilosante, polimiositis,

dermatomiositis, esclerosis sistémica, artritis idiopática juvenil, polimialgia reumática, Enfermedad de Sjogren, Histiocitosis de células de Langerhans (LCH), Enfermedad de Still, enfermedad intestinal inflamatoria, colitis ulcerativa, Enfermedad de Crohn, lupus eritematoso sistémico (LES), púrpura trombocitopénica inmune (PTI), mielopreparación para trasplante autólogo, rechazo de trasplante, enfermedad pulmonar obstructiva crónica (EPOC), enfisema, Enfermedad de Kawasaki, síndrome hemofagocítico (síndrome de macrófagos activados), reticulohistiocitosis multicéntrica y arterioesclerosis; trastornos metabólicos, incluyendo, pero no limitados a, Diabetes tipo I, Diabetes tipo II, resistencia a la insulina, hiperglicemia, obesidad y lipólisis; trastornos de la estructura ósea, mineralización y formación y resorción ósea, incluyendo, pero no limitadas a osteoporosis, osteodistrofia, aumento del riesgo de fractura, Enfermedad de Paget, hipercalcemia, osteolisis mediada por infección (osteomielitis, por ejemplo), y osteolisis periprotésica o desgaste mediado por residuos; enfermedades renales y genitourinarias, incluyendo, pero no limitadas a endometriosis, nefritis (por ejemplo, glomerulonefritis, nefritis intersticial, nefritis lúpica), necrosis renal tubular, complicaciones asociadas con la diabetes (por ejemplo, nefropatía diabética), e hipertrofia renal; trastornos del sistema nervioso, incluyendo, pero no limitados a desórdenes desmielinizantes (por ejemplo, esclerosis múltiple, Síndrome de Charcot Marie Tooth), esclerosis amiotrófica lateral (ALS), miasternia gravis, polineuropatía desmielinizante crónica, otros trastornos desmielinizantes, ataques, Enfermedad de Alzheimer y Enfermedad de Parkinson; dolor, incluyendo, pero no limitado a dolor crónico, dolor agudo, dolor inflamatorio, dolor neuropático, dolor en los huesos; enfermedades malignas, incluyendo, pero no limitadas a mieloma múltiple, leucemia mieloide aguda (LMA), leucemia mieloide crónica (LMC), cáncer de pulmón,

cáncer de páncreas, cáncer de próstata, cáncer de seno, cáncer de ovario, neuroblastoma, sarcoma, osteosarcoma, tumores de células gigantes, (por ejemplo, tumor de células gigantes del hueso, tumor de células gigantes de la vaina del tendón (TTCG)), sinovitis villonodular pigmentada (SVP), angiogénesis tumoral, melanoma, glioblastoma multiforme, glioma, otros tumores del sistema nervioso central, metástasis Cerebral, metástasis ósea, metástasis de tumores de otros tejidos y otras enfermedades mieloproliferativas crónicas como la mielofibrosis; vasculitis, incluyendo pero no limitadas a la enfermedad vascular de colágeno, poliarteritis nodosa, Enfermedad de Behcet, sarcoidosis, fiebre familiar mediterránea, Vasculitis Churg-Strauss, arteritis temporal, arteritis de células gigantes, Arteritis de Takayasu; indicaciones oftalmológicas, incluyendo pero no limitadas a uveitis, escleritis, retinitis, degeneración macular relacionada con la edad, neovascularización coroidea, retinopatía diabética; enfermedades hereditarias, incluyendo pero no limitadas a querubismo, neurofibromatosis; indicaciones de enfermedades infecciosas, incluyendo pero no limitadas a infecciones asociadas con el virus de inmunodeficiencia humana, virus de la hepatitis B, virus de la hepatitis C, anaplasmosis granulocítica humana; desórdenes de almacenamiento lisosomal, incluyendo pero no limitados a La enfermedad de Gaucher, Enfermedad de Fabry, Enfermedad de Niemann-Pick; indicaciones gastrointestinales, incluyendo pero no limitadas a cirrosis de hígado; indicaciones pulmonares, incluyendo pero no limitadas a fibrosis pulmonar, lesión pulmonar aguda (por ejemplo, inducidas por ventilador, humo o toxinas); isquemia global e indicaciones quirúrgicas, incluyendo pero no limitadas a (cardiopulmonar) cirugía de bypass, cirugía vascular e injertos vasculares.

[0448] En los aspectos y formas de realización que involucran el tratamiento o profilaxis de una enfermedad o condición con uno o más de los compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I, la invención suministra los métodos para tratar una enfermedad o condición mediada por Flt-3 En un sujeto con necesidad de éste (por ejemplo, un mamífero tal como un humano, otros primates, animales de deporte, animales de interés comercial tales como ganado, animales de finca tales como caballos o mascotas tales como perros y gatos), por ejemplo, una enfermedad o condición caracterizada por actividad Flt-3 anormal (por ejemplo, actividad de quinasa). En algunas formas de realización, los métodos de la invención pueden involucrar la administración al sujeto que sufre de una enfermedad o condición o está en riesgo de dicha enfermedad o condición mediada por Flt-3 una cantidad efectiva de uno o más compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I. En una de las formas de realización, la enfermedad mediada por Flt-3 se selecciona del grupo que consiste de enfermedades malignas, incluyendo, pero no limitadas a glioma, glioblastoma, metástasis cerebral, cáncer de pulmón, cáncer de seno, cáncer colorectal, cáncer de próstata, cáncer gástrico, cáncer esofageal, cáncer de páncreas, cáncer de ovario, linfoma no Hodgkin, Linfoma de Hodgkin, mieloma múltiple, leucemia linfocítica aguda, leucemia mieloide aguda, leucemia mieloide aguda con mielodisplasia en más de una línea, leucemia promielocítica aguda, leucemia linfocítica crónica, leucemia mieloide crónica, leucemia neutrofílica crónica, leucemia no diferenciada aguda, linfoma anaplásico de células grandes, leucemia prolinfocítica, leucemia mielomonocítica juvenil, leucemia linfocítica aguda de célula T en adultos, Leucemia linfocítica aguda de célula tipo T, Leucemia linfocítica aguda de célula B, leucemia de linaje mezclado, mieloma múltiple,

leucemia mielocítica crónica, leucemia linfoblástica aguda, leucemia mieloblástica aguda, leucemia mielomonocítica aguda; otras enfermedades incluyendo psoriasis, dermatitis atópica, degeneración axonal, mielitis transversa aguda, esclerosis amiotrófica lateral, atrofia muscular espinal juvenil, atrofia muscular espinal juvenil, Enfermedad de Creutzfeldt- Jakob, panencefalitis esclerosante subaguda, rechazo de órgano, rechazo de trasplante de médula ósea, rechazo de trasplante de médula ósea mieloablativa, espondilitis anquilosante, anemia aplásica, Enfermedad de Behcet, enfermedad de injerto vs huésped, Enfermedad de Graves, anemia hemolítica autoinmune, Granulomatosis de Wegener, síndrome de Hiper IgE, púrpura trombocitopénica idiopática, Miasternia gravis, diabetes mellitus tipo 1, artritis reumatoide, Enfermedad de Crohn, esclerosis múltiple, lupus eritematoso sistémico, síndrome mielodisplásico, trombocitemia, trombocitosis esencial, metaplasia mieloide angiogénica, mielofibrosis, mielofibrosis con metaplasia mieloide, mielofibrosis ideopática crónica, policitemia vera, anemia, leucopenia, neutropenia, trombocitopenia, granulocitopenia y pancitopenia.

[0449] En los aspectos y formas de realización que involucran el tratamiento o profilaxis de una enfermedad o condición con uno o más de los compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I, la invención suministra los métodos para tratar una enfermedad o condición mediada por Trk en un sujeto con necesidad de éste (por ejemplo, un mamífero tal como un humano, otros primates, animales de deporte, animales de interés comercial tales como ganado, animales de finca tales como caballos o mascotas tales como perros y gatos), por ejemplo, una enfermedad o condición caracterizada por actividad Trk anormal (por ejemplo, actividad de quinasa). En algunas formas de realización, los métodos de la invención pueden involucrar la administración al sujeto que sufre de

una enfermedad o condición o está en riesgo de dicha enfermedad o condición mediada por Trk una cantidad efectiva de uno o más compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I. En una de las formas de realización, la enfermedad mediada por Trk se selecciona del grupo que consiste de enfermedades malignas, incluyendo, pero no limitadas a cáncer de próstata, cáncer de pulmón microcítico, cáncer de pulmón no microcítico, Tumores de Wilms, nefroma mesoblástico, fibrosarcoma infantil, neuroblastoma, cáncer cerebral, cáncer de células escamosas, cáncer de vejiga, cáncer gástrico, cáncer de páncreas, cáncer de seno, cáncer de cabeza y cuello, cáncer esofageal, cáncer colorectal, cáncer de riñón, carcinoma hepatocelular, cáncer de ovario, cáncer ginecológico, cáncer de tiroides, cáncer cervical, tumor de ewing, tumores del sistema nervioso central y periférico, melanoma, mieloma múltiple, leucemia mielógena aguda y leucemia mieloide; neuropatías, incluyendo, pero no limitadas a ataques, esclerosis múltiple, Enfermedad de Parkinson, Enfermedad de Alzheimer, mielitis transversa y encefalitis; dolor, incluyendo, pero no limitadas a dolor crónico, dolor agudo, dolor inflamatorio, dolor neuropático y dolor asociado con cáncer, cirugía, o fractura de hueso; enfermedades óseas relacionadas, incluyendo, pero no limitadas a enfermedad metastásica ósea, pérdida ósea inducida por el tratamiento, osteoporosis, artritis reumatoide, espondilitis anquilosante, Enfermedad de Paget y enfermedad periodontal; otras enfermedades, incluyendo, pero no limitadas a asma, artritis, retinopatía diabética, degeneración macular, psoriasis, inflamación aguda y crónica, Sarcoma de Kaposi, haemangioma, nefropatias agudas y crónicas, ateroma, arterioesclerosis, estenosis arterial, fibrosarcoma, osteosarcoma, trastorno de pánico y enfermedad infecciosa (por ejemplo Infección por Tripanosoma cruzi (enfermedad de Chagas)).

[0450] En los aspectos y formas de realización que involucran el tratamiento o profilaxis de una enfermedad o condición, los métodos pueden involucrar la administración de una cantidad efectiva de uno o más compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I a un sujeto de necesidad de éstos sufriendo de o a riesgo de una enfermedad o condición seleccionada del grupo que consiste de artritis reumatoide, osteoartritis, osteoporosis, osteolisis periprotésica, esclerosis sistémica, desórdenes desmielinizantes, esclerosis múltiple, Síndrome de Charcot Marie Tooth, esclerosis amiotrófica lateral, Enfermedad de Alzheimer, Enfermedad de Parkinson, isquemia global, colitis ulcerativa, Enfermedad de Crohn, púrpura trombocitopénica inmune, arterioesclerosis, lupus eritematoso sistémico, mielopreparación para trasplante autólogo, rechazo de trasplante, glomerulonefritis, nefritis intersticial, Nefritis lúpica, necrosis renal tubular, nefropatía diabética, hipertrofía renal, diabetes tipo I, dolor agudo, dolor inflamatorio, dolor neuropático, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de seno, cáncer de próstata, cáncer de páncreas, cáncer de pulmón, cáncer de ovario, gliomas, glioblastomas, neurofibromatosis, metástasis ósea, metástasis cerebral, tumores estromales gastrointestinales, y tumores de células gigantes.

[0451] En los aspectos y formas de realización que involucran el tratamiento o profilaxis de una enfermedad o condición, los métodos pueden involucrar la administración de una cantidad efectiva de uno o más compuestos de la Fórmula I o una composición consiste de uno o más compuestos de la Fórmula I a un sujeto de necesidad de éstos, sufriendo de o a riesgo de una enfermedad o condición seleccionada del grupo que consiste de artritis reumatoide, osteoartritis, osteoporosis, osteolisis periprotésica, esclerosis múltiple, Enfermedad de Alzheimer,

Enfermedad de Parkinson, isquemia global, hipertrofía renal, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de seno, cáncer de próstata, cáncer de páncreas, glioblastoma, neurofibromatosis, metástasis cerebral, y tumores estromales gastrointestinales.

[0452] En los aspectos y formas de realización que involucran el tratamiento o profilaxis de una enfermedad o condición, los métodos pueden involucrar la administración de una cantidad efectiva de uno o más inhibidores Kit de la Fórmula I o una composición consiste de uno o más inhibidores Kit de la Fórmula I a un sujeto de necesidad de éstos, sufriendo de o a riesgo de una enfermedad o condición seleccionada del grupo que consiste de artritis reumatoide, tumores estromales gastrointestinales, melanoma y neurofibromatosis.

[0453] En los aspectos y formas de realización que involucran el tratamiento o profilaxis de una enfermedad o condición, los métodos pueden involucrar la administración de una cantidad efectiva de uno o más inhibidores selectivos Fms de la Fórmula I o una composición consiste de uno o mpas inhibidores selectivos de Fms de la Fórmula I a un sujeto de necesidad de éstos, sufriendo de o a riesgo de una enfermedad o condición seleccionada del grupo que consiste de esclerosis múltiple, Enfermedad de Alzheimer, Enfermedad de Parkinson, isquemia global, artritis reumatoide, osteoartritis, osteoporosis, osteolisis periprotésica, glomerulonefritis, nefritis intersticial, Nefritis lúpica, nefropatía diabética, e hipertrofía renal.

[0454] En los aspectos y formas de realización que involucran el tratamiento o profilaxis de una enfermedad o condición, los métodos pueden involucrar la administración de una cantidad efectiva de uno o más inhibidores selectivos Fms de la Fórmula I o una composición consiste de uno o más inhibidores selectivos Fms de

la Fórmula I a un sujeto de necesidad de éstos, sufriendo de o a riesgo de una enfermedad o condición seleccionada del grupo que consiste de esclerosis múltiple, Enfermedad de Alzheimer, Enfermedad de Parkinson e isquemia global, donde uno o más inhibidores selectivos de quinasa Fms cruzan de forma efectiva la barrera sangre-cerebro.

[0455] En los aspectos y formas de realización que involucran el tratamiento o profilaxis de una enfermedad o condición, los métodos pueden involucrar la administración de una cantidad efectiva de uno o más inhibidores selectivos Fms de la Fórmula I o una composición consiste de uno o más inhibidores selectivos Fms de la Fórmula I a un sujeto de necesidad de éstos, sufriendo de o a riesgo de una enfermedad o condición seleccionada del grupo que consiste de artritis reumatoide, osteoartritis, osteoporosis, osteolisis periprotésica, glomerulonefritis, nefritis intersticial, Nefritis lúpica, nefropatía diabética, hipertrofia renal, donde uno o más inhibidores selectivos de quinasa Fms no cruzan de forma efectiva la barrera sangre-cerebro.

[0456] En los aspectos y formas de realización que involucran el tratamiento o profilaxis de una enfermedad o condición, los métodos pueden involucrar la administración de una cantidad efectiva de uno o más inhibidores duales Fms/Kit de la Fórmula I o una composición consiste de uno o más inhibidores duales Fms/Kit de la Fórmula I a un sujeto de necesidad de éstos, sufriendo de o a riesgo de una enfermedad o condición seleccionada del grupo que consiste de cáncer de seno, cáncer de próstata, mieloma múltiple, melanoma, leucemia mieloide aguda, glioblastoma, metástasis cerebral, neurofibromatosis, tumores estromales gastrointestinales, artritis reumatoide, y esclerosis múltiple.

[0457] En los aspectos y formas de realización que involucran el tratamiento o

profilaxis de una enfermedad o condición, los métodos pueden involucrar la administración de una cantidad efectiva de uno o más inhibidores duales Fms/Flt-3 de la Fórmula I o una composición consiste de uno o más inhibidores duales Fms/Flt-3 de la Fórmula I a un sujeto de necesidad de éstos, sufriendo de o a riesgo de una enfermedad o condición seleccionada del grupo que consiste de cáncer de seno, cáncer de próstata, mieloma múltiple, melanoma, leucemia mieloide aguda, glioblastoma, metástasis cerebral, neurofibromatosis, tumores estromales gastrointestinales, artritis reumatoide, y esclerosis múltiple, preferiblemente donde la enfermedad es leucemia mieloide aguda.

[0458] En los aspectos y formas de realización que involucran el tratamiento o profilaxis de una enfermedad o condición, los métodos pueden involucrar la administración de una cantidad efectiva de uno o más inhibidores duales Fms/Trk de la Fórmula I o una composición consiste de uno o más inhibidores duales Fms/Trk de la Fórmula I a un sujeto de necesidad de éstos, sufriendo de o a riesgo de una enfermedad o condición seleccionada del grupo que consiste de cáncer de páncreas, cáncer de próstata y mieloma múltiple.

[0459] En un septuagésimo-tercero aspecto, uno o más compuestos de la Fórmula I se usarán en la preparación de un medicamento para el tratamiento de una enfermedad o condición relacionada con la quinasa tipo Kit seleccionada del grupo que consiste de procesos malignos que incluyen pero no se limitan a, mastocitoma, cáncer de pulmón microcítico, cáncer de pulmón no microcítico (NSCLC), cáncer de testículo, cáncer de páncreas, cáncer de seno, cáncer de próstata, carcinoma de células de merkel, carcinomas del tracto genital femenino, sarcomas de origen neuroectodermal, carcinoma colorectal, carcinoma in situ, tumores estromales gastrointestinales (GISTs), mieloma múltiple, angiogénesis tumoral, metástasis

cerebral, glioblastoma, astrocitoma, neuroblastoma, neurofibromatosis (incluyendo neoplasia de células de Schwann asociada con neurofibromatosis), leucemia mieloide aguda, leucemia linfocítica aguda, leucemia mieloide crónica, mastocitosis, melanoma y mastocitoma en perros; enfermedad cardiovascular, incluyendo pero no limitada a arterioesclerosis, cardiomiopatía, falla del corazón, hipertensión arterial pulmonar y fibrosis pulmonar; indicaciones inflamatorias y autoinmunes, incluyendo, pero no limitadas a alergia, anafilaxia, asma, artritis reumatoide, rinitis alérgica, esclerosis múltiple, enfermedad intestinal inflamatoria, rechazo de trasplante, hipereosinofilia, urticaria y dermatitis; indicaciones gastrointestinales, incluyendo pero no limitadas a enfermedad por reflujo gastroesofágico (ERGE), esofagitis y úlceras en el tracto gastrointestinal; indicaciones oftalmológicas, incluyendo pero no limitadas a uveitis y Retinitis; y indicaciones neurológicas, incluyendo pero no limitadas a migraña.

[0460] En un septuagésimo-cuarto aspecto, uno o más compuestos de la Fórmula I pueden usarse en la preparación de un medicamento para el tratamiento de una enfermedad o condición relacionada con la quinasa tipo Fms seleccionada del grupo que consiste de indicaciones inflamatorias y autoinmunes, incluyendo, pero no limitadas a artritis reumatoide, osteoartritis, artritis psoriásica, psoriasis, dermatitis, espondilitis anquilosante, polimiositis, dermatomiositis, esclerosis sistémica, artritis idiopática juvenil, polimialgia reumática, Enfermedad de Sjogren, Histiocitosis de células de Langerhans (LCH), Enfermedad de Still, enfermedad intestinal inflamatoria, colitis ulcerativa, Enfermedad de Crohn, lupus eritematoso sistémico (LES), púrpura trombocitopénica inmune (PTI), mielopreparación para trasplante autólogo, rechazo de trasplante, enfermedad pulmonar obstructiva crónica (EPOC), enfisema, Enfermedad de Kawasaki, síndrome hemofagocítico (síndrome de

macrófagos activados), reticulohistiocitosis multicéntrica y arterioesclerosis; trastornos metabólicos, incluyendo, pero no limitados a Diabetes tipo I, Diabetes tipo II, resistencia a la insulina, hiperglicemia, obesidad y lipólisis; trastornos de la estructura ósea, mineralización y formación y resorción ósea, incluyendo, pero no limitados a osteoporosis, osteodistrofia, aumento del riesgo de fractura, Enfermedad de Paget, hipercalcemia, osteolisis mediada por infección (osteomielitis, por ejemplo) y osteolisis periprotésica o desgaste mediado por residuos; enfermedades renales y genitourinarias, incluyendo, pero no limitadas a endometriosis, nefritis (por ejemplo, glomerulonefritis, nefritis intersticial, Nefritis lúpica), necrosis renal tubular, complicaciones asociadas con la diabetes (por ejemplo, nefropatía diabética) e hipertrofía renal; trastornos del sistema nervioso, incluyendo, pero no limitados a desórdenes desmielinizantes (por ejemplo, esclerosis múltiple, Síndrome de Charcot Marie Tooth), esclerosis amiotrófica lateral (ALS), miasternia gravis, polineuropatía desmielinizante crónica, otros trastornos desmielinizantes, ataques, Enfermedad de Alzheimer y Enfermedad de Parkinson; dolor, incluyendo, pero no limitado a dolor crónico, dolor agudo, dolor inflamatorio, dolor neuropático, dolor en los huesos; enfermedades malignas, incluyendo, pero no limitadas a mieloma múltiple, leucemia mieloide aguda (LMA), leucemia mieloide crónica (LMC), cáncer de pulmón, cáncer de páncreas, cáncer de próstata, cáncer de seno, cáncer de ovario, neuroblastoma, sarcoma, osteosarcoma, tumores de células gigantes, (por ejemplo, tumor de células gigantes del hueso, tumor de células gigantes de la vaina del tendón (TTCG)), sinovitis villonodular pigmentada (SVP), angiogénesis tumoral, melanoma, glioblastoma multiforme, glioma, otros tumores del sistema nervioso central, metástasis Cerebral, metástasis ósea, metástasis de tumores de otros tejidos, y otras enfermedades mieloproliferativas crónicas como la mielofibrosis; vasculitis,

incluyendo pero no limitada a la enfermedad vascular de colágeno, poliarteritis nodosa, Enfermedad de Behcet, sarcoidosis, fiebre familiar mediterránea, Vasculitis Churg-Strauss, arteritis temporal, arteritis de células gigantes, Arteritis de Takayasu; indicaciones oftalmológicas, incluyendo pero no limitadas a uveitis, escleritis, retinitis, degeneración macular relacionada con la edad, neovascularización coroidea, retinopatía diabética; enfermedades hereditarias, incluyendo pero no limitadas a querubismo, neurofibromatosis; indicaciones de enfermedades infecciosas, incluyendo pero no limitadas a infecciones asociadas con el virus de inmunodeficiencia humana, virus de la hepatitis B, virus de la hepatitis C, anaplasmosis granulocítica humana; desórdenes de almacenamiento lisosomal, incluyendo pero no limitados a la enfermedad de Gaucher, Enfermedad de Fabry, Enfermedad de Niemann-Pick; indicaciones gastrointestinales, incluyendo pero no limitadas a cirrosis de hígado; indicaciones pulmonares, incluyendo pero no limitadas a fibrosis pulmonar, lesión pulmonar aguda (por ejemplo, inducidas por ventilador, humo o toxinas); isquemia global, e indicaciones quirúrgicas, incluyendo pero no limitadas a (cardiopulmonar) cirugía de bypass, cirugía vascular e injertos vasculares.

[0461] En un septuagésimo-quinto aspecto, uno o más compuestos de la Fórmula I pueden usarse en la preparación de un medicamento para el tratamiento de una enfermedad o condición relacionada con la quinasa tipo Flt-3 seleccionada del grupo que consiste de procesos malignos que incluyen pero no se limitan a, glioma, glioblastoma, metástasis cerebral, cáncer de pulmón, cáncer de seno, cáncer colorectal, cáncer de próstata, cáncer gástrico, cáncer esofageal, cáncer de páncreas, cáncer de ovario, linfoma no Hodgkin, Linfoma de Hodgkin, mieloma múltiple, leucemia linfocítica aguda, leucemia mieloide aguda, leucemia mieloide aguda con

mielodisplasia en más de una línea, leucemia promielocítica aguda, leucemia linfocítica crónica, leucemia mieloide crónica, leucemia neutrofílica crónica, leucemia no diferenciada aguda, linfoma anaplásico de células grandes, leucemia prolinfocítica, leucemia mielomonocítica juvenil, leucemia linfocítica aguda de célula T en adultos, Leucemia linfocítica aguda de célula tipo T, Leucemia linfocítica aguda de célula B, leucemia de linaje mezclado, mieloma múltiple, leucemia mielocítica crónica, leucemia linfoblástica aguda, leucemia mieloblástica aguda, leucemia mielomonocítica aguda; otras enfermedades incluyendo psoriasis, dermatitis atópica, degeneración axonal, mielitis transversa aguda, esclerosis amiotrófica lateral, atrofia muscular espinal juvenil, atrofia muscular espinal juvenil, Enfermedad de Creutzfeldt- Jakob, panencefalitis esclerosante subaguda, rechazo de órgano, rechazo de trasplante de médula ósea, rechazo de trasplante de médula ósea mieloablativa, espondilitis anquilosante, anemia aplásica, Enfermedad de Behcet, enfermedad de injerto vs huésped, Enfermedad de Graves, anemia hemolítica autoinmune, Granulomatosis de Wegener, síndrome de Hiper IgE, púrpura trombocitopénica idiopática, Miasternia gravis, diabetes mellitus tipo 1, artritis reumatoide, Enfermedad de Crohn, esclerosis múltiple, lupus eritematoso sistémico, síndrome mielodisplásico, trombocitemia, trombocitosis esencial, metaplasia mieloide angiogénica, mielofibrosis, mielofibrosis con metaplasia mieloide, mielofibrosis ideopática crónica, policitemia vera, anemia, leucopenia, neutropenia, trombocitopenia, granulocitopenia y pancitopenia.

[0462] En un septuagésimo-sexto aspecto, uno o más compuestos de la Fórmula I pueden usarse en la preparación de un medicamento para el tratamiento de una enfermedad o condición relacionada con la quinasa tipo Trk seleccionada del grupo que consiste de procesos malignos que incluyen pero no se limitan a, cáncer de

próstata, cáncer de pulmón microcítico, cáncer de pulmón no microcítico, Tumores de Wilms, nefroma mesoblástico, fibrosarcoma infantil, neuroblastoma, cáncer cerebral, cáncer de células escamosas, cáncer de vejiga, cáncer gástrico, cáncer de páncreas, cáncer de seno, cáncer de cabeza y cuello, cáncer esofageal, cáncer colorectal, cáncer de riñón, carcinoma hepatocelular, cáncer de ovario, cáncer ginecológico, cáncer de tiroides, cáncer cervical, tumor de ewing, tumores del sistema nervioso central y periférico, melanoma, mieloma múltiple, leucemia mielógena aguda, y leucemia mieloide; neuropatias, incluyendo, pero no limitadas a ataques, esclerosis múltiple, Enfermedad de Parkinson, Enfermedad de Alzheimer, mielitis transversa y encefalitis; dolor, incluyendo, pero no limitado a dolor crónico, dolor agudo, dolor inflamatorio, dolor neuropático y dolor asociado con cáncer, cirugía, o fractura de hueso; enfermedades óseas relacionadas, incluyendo, pero no limitadas a enfermedad metastásica ósea, pérdida ósea inducida por el tratamiento, osteoporosis, artritis reumatoide, espondilitis anquilosante, Enfermedad de Paget, y enfermedad periodontal; otras enfermedades, incluyendo, pero no limitadas a asma, artritis, retinopatía diabética, degeneración macular, psoriasis, inflamación aguda y crónica, Sarcoma de Kaposi, haemangioma, nefropatias agudas y crónicas, ateroma, arterioesclerosis, estenosis arterial, fibrosarcoma, osteosarcoma, trastorno de pánico, y enfermedad infecciosa (por ejemplo Infección por Tripanosoma cruzi (enfermedad de Chagas)).

[0463] En un septuagésimo-séptimo aspecto, uno o más compuestos de la Fórmula I pueden usarse en la preparación de un medicamento para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de artritis reumatoide, osteoartritis, osteoporosis, osteolisis periprotésica, esclerosis sistémica, desórdenes desmielinizantes, esclerosis múltiple, Síndrome de Charcot Marie Tooth, esclerosis

amiotrófica lateral, Enfermedad de Alzheimer, Enfermedad de Parkinson, isquemia global, colitis ulcerativa, Enfermedad de Crohn, púrpura trombocitopénica inmune, arterioesclerosis, lupus eritematoso sistémico, mielopreparación para trasplante autólogo, rechazo de trasplante, glomerulonefritis, nefritis intersticial, Nefritis lúpica, necrosis renal tubular, nefropatía diabética, hipertrofía renal, diabetes tipo I, dolor agudo, dolor inflamatorio, dolor neuropático, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de seno, cáncer de próstata, cáncer de páncreas, cáncer de pulmón, cáncer de ovario, gliomas, glioblastomas, neurofibromatosis, metástasis ósea, metástasis cerebral, tumores estromales gastrointestinales, y tumores de células gigantes.

[0464] En un septuagésimo-octavo aspecto, uno o más compuestos de la Fórmula I pueden usarse en la preparación de un medicamento para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de artritis reumatoide, osteoartritis, osteoporosis, osteolisis periprotésica, esclerosis múltiple, Enfermedad de Alzheimer, Enfermedad de Parkinson, isquemia global, hipertrofía renal, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de seno, cáncer de próstata, cáncer de páncreas, glioblastoma, neurofibromatosis, metástasis cerebral, y tumores estromales gastrointestinales.

[0465] En un septuagésimo-noveno aspecto, uno o más compuestos como los descritos aquí, que son Inhibidores de la quinasa tipo Kit pueden usarse en la preparación de un medicamento para el tratamiento de artritis reumatoide, tumores estromales gastrointestinales, melanoma o neurofibromatosis.

[0466] En un octogésimo aspecto, uno o más compuestos como los descritos aquí, que son inhibidores selectivos Fms pueden usarse en la preparación de un medicamento para el tratamiento de esclerosis múltiple, Enfermedad de Alzheimer,

Enfermedad de Parkinson, isquemia global, artritis reumatoide, osteoartritis, osteoporosis, osteolisis periprotésica, glomerulonefritis, nefritis intersticial, Nefritis lúpica, nefropatía diabética o hipertrofía renal.

[0467] En un octogésimo-primero aspecto, uno o más compuestos como los descritos aquí, que son inhibidores selectivos de quinasa Fms que cruzan de forma efectiva la barrera sangre-cerebro pueden usarse en la preparación de un medicamento para el tratamiento de esclerosis múltiple, glioblastoma, Enfermedad de Alzheimer, Enfermedad de Parkinson o isquemia global.

[0468] En un octogésimo-segundo aspecto, uno o más compuestos como los descritos aquí, que son inhibidores selectivos de quinasa Fms que no cruzan de forma efectiva la barrera sangre-cerebro pueden usarse en la preparación de un medicamento para el tratamiento de artritis reumatoide, osteoartritis, osteoporosis, osteolisis periprotésica, glomerulonefritis, nefritis intersticial, Nefritis lúpica, nefropatía diabética o hipertrofía renal.

[0469] En un octogésimo-tercero aspecto, uno o más compuestos como los descritos aquí, que son inhibidores selectivos duales Fms / Inhibidores de la quinasa tipo Kit pueden usarse en la preparación de un medicamento para el tratamiento de cáncer de seno, cáncer de próstata, mieloma múltiple, melanoma, leucemia mieloide aguda, glioblastoma, metástasis cerebral, neurofibromatosis, tumores estromales gastrointestinales, artritis reumatoide o esclerosis múltiple.

[0470] En un octogésimo-cuarto aspecto, uno o más compuestos como los descritos aquí, que son inhibidores selectivos duales Fms/Flt-3 pueden usarse en la preparación de un medicamento para el tratamiento de cáncer de seno, cáncer de próstata, mieloma múltiple, melanoma, leucemia mieloide aguda, glioblastoma, metástasis cerebral, neurofibromatosis, tumores estromales gastrointestinales, artritis

reumatoide o esclerosis múltiple, preferiblemente en donde la enfermedad es leucemia mieloide aguda.

[0471] En un octogésimo-quinto aspecto, uno o más compuestos como los descritos aquí, que son inhibidores selectivos duales Fms/Trk pueden usarse en la preparación de un medicamento para el tratamiento de cáncer de páncreas, cáncer de próstata, y mieloma múltiple.

[0472] En un octogésimo-sexto aspecto, se proporcionan compuestos de la Fórmula I para el tratamiento de una enfermedad o condición relacionada con la quinasa tipo Kit seleccionada del grupo que consiste de procesos malignos que incluyen pero no se limitan a, mastocitoma, cáncer de pulmón microcítico, cáncer de pulmón no microcítico (NSCLC), cáncer de testículo, cáncer de páncreas, cáncer de seno, cáncer de próstata, carcinoma de células de merkel, carcinomas del tracto genital femenino, sarcomas de origen neuroectodermal, carcinoma colorectal, carcinoma in situ, tumores estromales gastrointestinales (GISTs), mieloma múltiple, angiogénesis tumoral, metástasis cerebral, glioblastoma, astrocitoma, neuroblastoma, neurofibromatosis (incluyendo neoplasia de células de Schwann asociada con neurofibromatosis), leucemia mieloide aguda, leucemia linfocítica aguda, leucemia mieloide crónica, mastocitosis, melanoma y mastocitoma en perros; enfermedad cardiovascular, incluyendo pero no limitada a arterioesclerosis, cardiomiopatía, falla del corazón, hipertensión arterial pulmonar y fibrosis pulmonar; indicaciones inflamatorias y autoinmunes, incluyendo, pero no limitadas a alergia, anafilaxia, asma, artritis reumatoide, rinitis alérgica, esclerosis múltiple, enfermedad intestinal inflamatoria, rechazo de trasplante, hipereosinofilia, urticaria y dermatitis; indicaciones gastrointestinales, incluyendo pero no limitadas a enfermedad por reflujo gastroesofágico (ERGE), esofagitis y úlceras en el tracto

gastrointestinal; indicaciones oftalmológicas, incluyendo pero no limitadas a uveitis y Retinitis; e indicaciones neurológicas, incluyendo pero no limitadas a migraña.

[0473] En un octogésimo-séptimo aspecto se proporcionan compuestos de la Fórmula I para el tratamiento de una enfermedad o condición relacionada con la quinasa tipo Fms seleccionada del grupo que consiste de indicaciones inflamatorias y autoinmunes, incluyendo, pero no limitadas a artritis reumatoide, osteoartritis, artritis psoriásica, psoriasis, dermatitis, espondilitis anquilosante, polimiositis, dermatomiositis, esclerosis sistémica, artritis idiopática juvenil, polimialgia reumática, Enfermedad de Sjogren, Histiocitosis de células de Langerhans (LCH), Enfermedad de Still, enfermedad intestinal inflamatoria, colitis ulcerativa, Enfermedad de Crohn, lupus eritematoso sistémico (LES), púrpura trombocitopénica inmune (PTI), mielopreparación para trasplante autólogo, rechazo de trasplante, enfermedad pulmonar obstructiva crónica (EPOC), enfisema, Enfermedad de Kawasaki, síndrome hemofagocítico (síndrome de macrófagos activados), reticulohistiocitosis multicéntrica y arterioesclerosis; trastornos metabólicos, incluyendo, pero no limitados a Diabetes tipo I, Diabetes tipo II, resistencia a la insulina, hiperglicemia, obesidad y lipólisis; trastornos de la estructura ósea, mineralización y formación y resorción ósea, incluyendo, pero no limitados a osteoporosis, osteodistrofia, aumento del riesgo de fractura, Enfermedad de Paget, hipercalcemia, osteolisis mediada por infección (osteomielitis, por ejemplo), y osteolisis periprotésica o desgaste mediado por residuos; enfermedades renales y genitourinarias, incluyendo, pero no limitadas a endometriosis, nefritis (por ejemplo, glomerulonefritis, nefritis intersticial, Nefritis lúpica), necrosis renal tubular, complicaciones asociadas con la diabetes (por ejemplo, nefropatía diabética), e hipertrofia renal; trastornos del sistema nervioso, incluyendo, pero no limitados a

desórdenes desmielinizantes (por ejemplo, esclerosis múltiple, Síndrome de Charcot Marie Tooth), esclerosis amiotrófica lateral (ALS), miasternia gravis, polineuropatía desmielinizante crónica, otros trastornos desmielinizantes, ataques, Enfermedad de Alzheimer y Enfermedad de Parkinson; dolor, incluyendo, pero no limitado a dolor crónico, dolor agudo, dolor inflamatorio, dolor neuropático, dolor en los huesos; enfermedades malignas, incluyendo, pero no limitadas a to, mieloma múltiple, leucemia mieloide aguda (LMA), leucemia mieloide crónica (LMC), cáncer de pulmón, cáncer de páncreas, cáncer de próstata, cáncer de seno, cáncer de ovario, neuroblastoma, sarcoma, osteosarcoma, tumores de células gigantes, (por ejemplo, tumor de células gigantes del hueso, tumor de células gigantes de la vaina del tendón (TTCG)), sinovitis villonodular pigmentada (SVP), angiogénesis tumoral, melanoma, glioblastoma multiforme, glioma, otros tumores del sistema nervioso central, metástasis cerebral, metástasis ósea, metástasis de tumores de otros tejidos, y otras enfermedades mieloproliferativas crónicas como la mielofibrosis; vasculitis, incluyendo pero no limitadas a la enfermedad vascular de colágeno, poliarteritis nodosa, Enfermedad de Behcet, sarcoidosis, fiebre familiar mediterránea, Vasculitis Churg-Strauss, arteritis temporal, arteritis de células gigantes, Arteritis de Takayasu; indicaciones oftalmológicas, incluyendo pero no limitadas a uveitis, escleritis, retinitis, degeneración macular relacionada con la edad, neovascularización coroidea, retinopatía diabética; enfermedades hereditarias, incluyendo pero no limitadas a querubismo, neurofibromatosis; indicaciones de enfermedades infecciosas, incluyendo pero no limitadas a infecciones asociadas con el virus de inmunodeficiencia humana, virus de la hepatitis B, virus de la hepatitis C, anaplasmosis granulocítica humana; desórdenes de almacenamiento lisosomal, incluyendo pero no limitado a la enfermedad de Gaucher, Enfermedad de Fabry,

Enfermedad de Niemann-Pick; indicaciones gastrointestinales, including pero no limitadas a to cirrosis de hígado; indicaciones pulmonares, incluyendo pero no limitadas a fibrosis pulmonar, lesión pulmonar aguda (por ejemplo, inducidas por ventilador, humo o toxinas); isquemia global, e indicaciones quirúrgicas, incluyendo pero no limitadas a (cardiopulmonar) cirugía de bypass, cirugía vascular e injertos vasculares.

[0474] En un octogésimo-octavo aspecto, se proporcionan compuestos de la Fórmula I para el tratamiento de una enfermedad o condición relacionada con la quinasa tipo Flt-3 seleccionada del grupo que consiste de procesos malignos que incluyen pero no se limitan a glioma, glioblastoma, metástasis cerebral, cáncer de pulmón, cáncer de seno, cáncer colorectal, cáncer de próstata, cáncer gástrico, cáncer esofageal, cáncer de páncreas, cáncer de ovario, linfoma no Hodgkin, Linfoma de Hodgkin, mieloma múltiple, leucemia linfocítica aguda, leucemia mieloide aguda, leucemia mieloide aguda con mielodisplasia en más de una línea, leucemia promielocítica aguda, leucemia linfocítica crónica, leucemia mieloide crónica, leucemia neutrofílica crónica, leucemia no diferenciada aguda, linfoma anaplásico de células grandes, leucemia prolinfocítica, leucemia mielomonocítica juvenil, leucemia linfocítica aguda de célula T en adultos, Leucemia linfocítica aguda de célula tipo T, Leucemia linfocítica aguda de célula B, leucemia de linaje mezclado, mieloma múltiple, leucemia mielocítica crónica, leucemia linfoblástica aguda, leucemia mieloblástica aguda, leucemia mielomonocítica aguda; otras enfermedades incluyendo psoriasis, dermatitis atópica, degeneración axonal, mielitis transversa aguda, esclerosis amiotrófica lateral, atrofia muscular espinal juvenil, atrofia muscular espinal juvenil, Enfermedad de Creutzfeldt- Jakob, panencefalitis esclerosante subaguda, rechazo de órgano, rechazo de trasplante de médula ósea,

rechazo de trasplante de médula ósea mieloablativa, espondilitis anquilosante, anemia aplásica, Enfermedad de Behcet, enfermedad de injerto vs huésped, Enfermedad de Graves, anemia hemolítica autoinmune, Granulomatosis de Wegener, síndrome de Hiper IgE, púrpura trombocitopénica idiopática, Miasternia gravis, diabetes mellitus tipo 1, artritis reumatoide, Enfermedad de Crohn, esclerosis múltiple, lupus eritematoso sistémico, síndrome mielodisplásico, trombocitemia, trombocitosis esencial, metaplasia mieloide angiogénica, mielofibrosis, mielofibrosis con metaplasia mieloide, mielofibrosis ideopática crónica, policitemia vera, anemia, leucopenia, neutropenia, trombocitopenia, granulocitopenia y pancitopenia.

[0475] En un octogésimo noveno aspecto, se proporcionan compuestos de la Fórmula I para el tratamiento de una enfermedad o condición relacionada con la quinasa tipo Trk seleccionada del grupo que consiste de procesos malignos que incluyen pero no se limitan a, cáncer de próstata, cáncer de pulmón microcítico, cáncer de pulmón no microcítico, Tumores de Wilms, nefroma mesoblástico, fibrosarcoma infantil, neuroblastoma, cáncer cerebral, cáncer de células escamosas, cáncer de vejiga, cáncer gástrico, cáncer de páncreas, cáncer de seno, cáncer de cabeza y cuello, cáncer esofageal, cáncer colorectal, cáncer de riñón, carcinoma hepatocelular, cáncer de ovario, cáncer ginecológico, cáncer de tiroides, cáncer cervical, tumor de ewing, tumores del sistema nervioso central y periférico, melanoma, mieloma múltiple, leucemia mielógena aguda, y leucemia mieloide; neuropatias, incluyendo, pero no limitadas a ataques, esclerosis múltiple, Enfermedad de Parkinson, Enfermedad de Alzheimer, mielitis transversa y encefalitis; dolor, incluyendo, pero no limitado a dolor crónico, dolor agudo, dolor inflamatorio, dolor neuropático y dolor asociado con cáncer, cirugía, o fractura de

hueso; enfermedades óseas relacionadas, incluyendo, pero no limitadas a enfermedad metastásica ósea, pérdida ósea inducida por el tratamiento, osteoporosis, artritis reumatoide, espondilitis anquilosante, Enfermedad de Paget, y enfermedad periodontal; otras enfermedades, incluyendo, pero no limitadas a to, asma, artritis, retinopatía diabética, degeneración macular, psoriasis, inflamación aguda y crónica, Sarcoma de Kaposi, haemangioma, nefropatias agudas y crónicas, ateroma, arterioesclerosis, estenosis arterial, fibrosarcoma, osteosarcoma, trastorno de pánico, y enfermedad infecciosa (por ejemplo, Infección por Tripanosoma cruzi (enfermedad de Chagas)).

[0476] En un nonagésimo aspecto, se proporcionan compuestos de la Fórmula I para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de artritis reumatoide, osteoartritis, osteoporosis, osteolisis periprotésica, esclerosis sistémica, desórdenes desmielinizantes, esclerosis múltiple, Síndrome de Charcot Marie Tooth, esclerosis amiotrófica lateral, Enfermedad de Alzheimer, Enfermedad de Parkinson, isquemia global, colitis ulcerativa, Enfermedad de Crohn, púrpura trombocitopénica inmune, arterioesclerosis, lupus eritematoso sistémico, mielopreparación para trasplante autólogo, rechazo de trasplante, glomerulonefritis, nefritis intersticial, Nefritis lúpica, necrosis renal tubular, nefropatía diabética, hipertrofía renal, diabetes tipo I, dolor agudo, dolor inflamatorio, dolor neuropático, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de seno, cáncer de próstata, cáncer de páncreas, cáncer de pulmón, cáncer de ovario, gliomas, glioblastomas, neurofibromatosis, metástasis ósea, metástasis cerebral, tumores estromales gastrointestinales y tumores de células gigantes.

[0477] En un nonagésimo primer aspecto, se proporcionan compuestos de la Fórmula I para el tratamiento de una enfermedad o condición seleccionada del grupo

que consiste de artritis reumatoide, osteoartritis, osteoporosis, osteolisis periprotésica, esclerosis múltiple, Enfermedad de Alzheimer, Enfermedad de Parkinson, isquemia global, hipertrofía renal, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de seno, cáncer de próstata, cáncer de páncreas, glioblastoma, neurofibromatosis, metástasis cerebral, y tumores estromales gastrointestinales.

[0478] En un nonagésimo segundo aspecto, se proporcionan compuestos como los aquí descritos que son Inhibidores de la quinasa tipo Kit para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de artritis reumatoide, tumores estromales gastrointestinales, melanoma y neurofibromatosis.

[0479] En un nonagésimo tercer aspecto, se proporcionan compuestos como los aquí descritos que son inhibidores selectivos Fms para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de esclerosis múltiple, Enfermedad de Alzheimer, Enfermedad de Parkinson, isquemia global, artritis reumatoide, osteoartritis, osteoporosis, osteolisis periprotésica, glomerulonefritis, nefritis intersticial, Nefritis lúpica, nefropatía diabética e hipertrofía renal.

[0480] En un nonagésimo cuarto aspecto, se proporcionan compuestos como los aquí descritos que son inhibidores selectivos de quinasa Fms que cruzan de forma efectiva la barrera sangre-cerebro para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de esclerosis múltiple, glioblastoma, Enfermedad de Alzheimer, Enfermedad de Parkinson, y isquemia global.

[0481] En un nonagésimo quinto aspecto, se proporcionan compuestos como los aquí descritos que son inhibidores selectivos de quinasa Fms que no cruzan de forma efectiva la barrera sangre-cerebro para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de artritis reumatoide, osteoartritis,

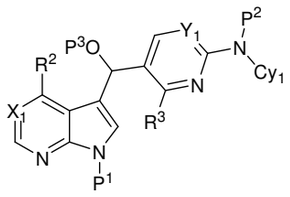
osteoporosis, osteolisis periprotésica, glomerulonefritis, nefritis intersticial, Nefritis lúpica, nefropatía diabética e hipertrofia renal.

[0482] En un nonagésimo sexto aspecto, se proveen compuestos como los aquí descritos que son inhibidores duales de Fms/Kit para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de cáncer de seno, cáncer de próstata, mieloma múltiple, melanoma, leucemia mieloide aguda, gliobastoma, metástasis Cerebral, neurofibromatosis, tumores estromales gastrointestinales, artritis Reumatoide y esclerosis múltiple

[0483 En un nonagésimo séptimo aspecto, se proveen compuestos como los aquí descritos que son inhibidores duales de Fms/Flt-3 para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de cáncer de seno, cáncer de próstata, mieloma múltiple, melanoma, leucemia mieloide aguda, gliobastoma, metástasis Cerebral, neurofibromatosis, tumores estromales gastrointestinales, artritis Reumatoide y esclerosis múltiple, preferiblemente donde la enfermedad es leucemia mieloide aguda.

[0484] En un nonagésimo octavo aspecto, se proveen compuestos como los aquí descritos que son inhibidores duales de las Fms/Trk para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de cáncer pancreático, cáncer de próstata, y mieloma múltiple.

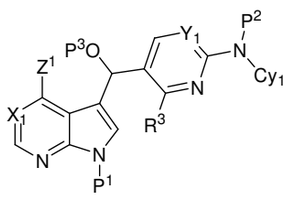
[0485] En un nonagésimo noveno aspecto, la invención provee un compuesto de la Fórmula II:



(II)

Donde P^1 y P^2 son cada uno de forma independiente H son cada uno de forma independiente un grupo protector de amino. P3 es H o un grupo protector de hidroxilo o un grupo lábil. En una de las formas de realización, P^1 y P^2 son cada uno de forma independiente un grupo protector de amino. En una de las formas de realización, P^3 es H. Todas las otras variables X_1, R^2, R^3, Y_1 y Ci_1 son como lo define cualquier de las formas de realización de la fórmula I aquí descrita.

[0486] En un centésimo aspecto, la invención provee un compuesto de la Fórmula IIa:

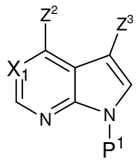


IIa

Donde P^1 y P^2 son cada uno de forma independiente H y son cada uno de forma independiente un grupo protector de amino. P3 es H o un grupo protector de hidroxilo o un grupo lábil. Z^1 es Br, Cl o R^2, donde R^2 es como se define en cualquier de las formas de realización de la fórmula I aquí descrita. En una de las formas de realización, Z^1 es Cl o Br. En una de las formas de realización, P^1 y P^2 son cada uno de forma independiente un grupo protector de amino. En una de las formas de realización, P^3 es H. Todas las otras variables X_1, R^3, Y_1 y Ci_1 son como lo define cualquier de las formas de realización de la fórmula I aquí descrita.

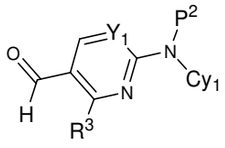
[0487] En un centésimo primer aspecto, la invención provee un método para preparar un compuesto de la Fórmula I. El método incluye contactar un compuesto de la Fórmula II con un agente bajo condiciones suficientes para forma un compuesto de la Fórmula I. El agente puede ser un agente oxidizante o reductor. Los ejemplos del agente oxidizante incluyen, pero no están limitados a, Periodinano de Dess-Martin (DMP). Los ejemplos de agentes reductores incluyen, pero no están limitados a, trialquilsilano. En algunas formas de realización, el método proporcionado para preparar cualquier de los compuestos descritos en las Tablas 1 o 2, o cualquiera de los compuestos de la Fórmula I o cualquiera de los compuestos aquí descritos.

[0488] En un centésimo segundo aspecto, la invención provee un método para preparar un compuesto de la Fórmula II o IIa. El método incluye conectar un compuesto de la Fórmula III:



III

Con un compuesto de la FórmulaIV:



IV

Bajo condiciones suficientes para formar un compuesto de la Fórmula II o IIa, donde Z^2 es Br, Cl o R^2 como se define en cualquiera de las formas de realización aquí descritas; Z^3 es yodo, a grupo saliente o a Grupo Lábil; P^1 y P^2 son cada uno de forma independiente un grupo protector de amino. En una de las formas de

realización, Z^2 es Cl o Br y Z^3 es I. En otra forma de realización, Z^2 es R^2. En algunas formas de realización, Z^3 es yodo, metanosulfoniloxi, p-toluenosulfoniloxi, triflúorometanosulfoniloxi. Todas las otras variables X_1, R^3, Y_1 y Ci_1 son como lo define cualquiera de las formas de realización de la fórmula I aquí descrita. En algunas formas de realización, el método es proporcionado para preparar cualquiera de los compuestos descritos en las Tablas 1 o 2, o cualquiera de los compuestos de la Fórmula I o cualquiera de los compuestos aquí descritos. En algunas formas de realización, los compuestos de la fórmula IV son un aldehído seleccionado de los descritos en las Tablas 3, 4, 5 y/o 6. En algunas formas de realización, los compuestos de la fórmula III es un compuesto de pirrolo [2,3-b] piridina seleccionado de los descritos en las Tablas 4, 5 y/o 6. En algunas formas de realización, los compuestos de la fórmula IV son pirrolo [2,3-b] pirimidina seleccionado de los descritos en la Tabla 5.

[0489] Alguno o más de los compuestos de la fórmula I demuestran actividad inhibitoria de una o más quinasas tipo Fms, Kit, Flt3 y Trk, incluyendo perfiles de actividad deseables como los aquí descritos con selectividad relativa a las otras quinasas. Los compuestos de la fórmula I también demuestran una o más propiedades deseables, incluyendo mejoramiento de las propiedades farmacocinéticas, solubilidad favorable, falta de inhibición de Cip favorable, y similares.

[0490] Los aspectos y formas de realización serán aparentes a partir de la siguiente Descripción Detallada de la invención y de las reivindicaciones.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

[0491] Como se usa aquí las siguientes definiciones aplican a menos que se indique claramente lo contrario:

[0492] Se tiene en cuenta aquí que como se usa en esta especificación y en las reivindicaciones adjuntas, las formas en singular “un” “uno” “una” y “la” “el” incluyen la referencia en plural a menos que se indique lo contrario.

[0493] Todos los átomos designados dentro de una Fórmula aquí descrita, ya sea dentro de una estructura suministrada, o dentro de las definiciones de las variables relacionadas con la estructura, también incluyen los isótopos de los mismos, a menos que se indique lo contrario. Se entiende que para cualquier átomo dado, los isótopos pueden estar presentes esencialmente en los radios+ de acuerdo a su ocurrencia natural, o uno o más átomos particulares pueden ser enriquecidos con respecto a uno o más isótopos usando métodos sintéticos conocidos por aquellos versados en el arte. De esta forma, 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; sulfuro incluye por ejemplo ^{32}S, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{37}S, ^{38}S; flúor incluye por ejemplo ^{17}F, ^{18}F, ^{19}F; cloro incluye por ejemplo ^{35}Cl, ^{36}Cl, ^{37}Cl, ^{38}Cl, ^{39}Cl; y similarmente.

[0494] “Halógeno” se refiere a todos los halógenos, a saber, cloro (Cl), flúor (F), bromo (Br), o yodo (I).

[0495] "Haloalquilo," incluye al alquilo sustituido por uno a siete átomos halógenos. Haloalquilo incluye monohaloalquilo y Polihaloalquilo. Por ejemplo, el

término "C_{1-6} haloalquilo" incluye triflúorometil, diflúorometil, 2,2,2-triflúoroetil, 4-clorobutil, 3-bromopropil, y similarmente.

[0496] “Hidroxilo” o "hidroxi" se refieren al grupo -OH.

[[0497] “Tiol” se refiere al grupo -SH.

[0498] “Alquilo inferior” solo o en combinación significa un radical derivado de un alcano que contiene de 1 a 6 átomos de carbono(a menos que se defina específicamente) que incluye un alquilo de cadena recta o un alquilo ramificado. (A menos que se defina específicamente) que incluye un alquilo de cadena recta o un alquilo ramificado. El grupo de alquilo inferior de cadena recta o ramificado es químicamente factible y enlazado a cualquier punto disponible para suministrar un compuesto estable. En muchas formas de realización, un alquilo inferior es un grupo de alquilos rectos o ramificados que contienen de 1-6, 1-4,1-3 o 1-2, átomos de carbono, tales como el metil, etil, propilo, isopropil, butil, t-butil y similares. En algunos casos, se especifica la opción del número de átomos de carbono en un alquilo inferior, por ejemplo, C_{1-3} alquilo se refiere al alquilo inferior que tiene 1, 2 o 3 átomos de carbono. Un "un alquilo inferior sustituido" denota un alquilo inferior que es sustituido independientemente, a menos que se indique lo contrario, con uno o más, preferiblemente 1, 2, 3, 4, 5 o 6, también 1, 2, o 3 sustitutos, como los aquí descritos, adheridos a cualquier átomo disponible para proporcionar un compuesto estable. Por ejemplo un “alquilo inferior sustituido con flúor” denota al grupo del alquilo inferior sustituido con uno o más átomos de flúor, tal como perflúoralquilo, donde preferiblemente el alquilo inferior es sustituido con 1, 2, 3, 4, 5 o 6 átomos de flúor, también 1, 2, o 3 átomos de flúor. Se entiende que dichas sustituciones son

químicamente factibles y enlazables con cualquier átomo disponible para suministrar un compuesto estable.

[0499] Alcoxi inferior" denota el grupo -OR^a, donde R^a es un alquilo inferior. En algunos casos, se especifica la opción del número de átomos de carbono en el alcoxi inferior, por ejemplo, alkoxi C_{1-3} se refiere al alkoxi inferior que tiene 1, 2 o 3 átomos de carbono. "Alcoxi inferior sustituido" denota al alcoxi inferior en el que R^z es un alquilo inferior sustituido con uno o más sustitutos como los aquí descritos, por ejemplo, en la descripción de los compuestos de la fórmula I, incluyendo las descripciones del cicloalquilo sustituido, el fenil y el heteroaril, se adhieren a cualquier átomo disponible para proporcionar un compuesto estable. Preferiblemente, la sustitución del alcoxi inferior es con 1, 2, 3, 4, 5 o 6 sustitutos, también 1, 2, o 3 sustitutos. Por ejemplo "el alcoxi inferior sustituido con flúor" denota al alcoxi inferior en el cual el alquilo inferior es sustituido con uno o más átomos de flúor, donde preferiblemente el alcoxi inferior es sustituido con 1, 2, 3, 4, 5 o 6 átomos de flúor, también 1, 2, o 3 átomos de flúor. Se entiende que dichas sustituciones son químicamente factibles y enlazables con cualquier átomo disponible para suministrar un compuesto estable.

[0500] "Alquiltio inferior" denota el grupo –SR^b, dondeR^b es alquilo inferior. En algunos casos, se especifica el número de átomos de carbono en el alquilo inferior, por ejemplo, alquiltio C_{1-3} se refiere al Alquiltio inferior que tiene 1, 2 o 3 átomos de carbono. "Un alquiltio inferior sustituido" denota un Alquiltio inferior en el cual R^z es el alquilo inferior sustituido con uno o más sustitutos como los aquí descritos, por ejemplo, en la descripción de los compuestos de la fórmula I, incluyendo las

descripciones del cicloalquilo sustituido, el fenil y el heteroaril, se adhieren a cualquier átomo disponible para proporcionar un compuesto estable. Preferiblemente, la sustitución del Alquiltio inferior es con 1, 2, 3, 4, 5 o 6 sustitutos, también 1, 2, o 3 sustitutos. Por ejemplo “el alquiltio inferior sustituido con flúor” denota al alquiltio inferior en el cual el alquilo inferior es sustituido con uno o más átomos de flúor, donde preferiblemente el alquiltio inferior es sustituido con 1, 2, 3, 4, 5 o 6 átomos de flúor, también 1, 2, o 3 átomos de flúor. Se entiende que dichas sustituciones son químicamente factibles y enlazables con cualquier átomo disponible para suministrar un compuesto estable.

[0501] “Alquilsulfonil inferior” denota el grupo $–S(O)_2R^c$, dondeR^c es alquilo inferior. En algunos casos, se especifica el número de átomos de carbono en el alquilo inferior, por ejemplo, C_{1-3} alquilosulfonil se refiere al alquilsulfonil inferior que tiene 1, 2 o 3 átomos de carbono. "Un alquilosulfonil inferior sustituido” denota al alquilsulfonil inferior en el cual R^z es alquilo inferior sustituido con uno o más sustitutos como los aquí descritos, por ejemplo, en la descripción de los compuestos de la fórmula I, incluyendo las descripciones del cicloalquilo sustituido, el fenil y el heteroaril, se adhieren a cualquier átomo disponible para proporcionar un compuesto estable. Preferiblemente, la sustitución del Alquilsulfonil inferior es con 1, 2, 3, 4, 5 o 6 sustitutos, también 1, 2, o 3 sustitutos. Por ejemplo “alquilsulfonil inferior sustituido con flúor” denota al alquilsulfonil inferior en el cual el alquilo inferior es sustituido con uno o más átomos de flúor, donde preferiblemente el alquilsulfonil inferior es sustituido con 1, 2, 3, 4, 5 o 6 átomos de flúor, también 1, 2, o 3 átomos de flúor. Se entiende que dichas sustituciones son

químicamente factibles y enlazables con cualquier átomo disponible para suministrar un compuesto estable.

[0502] "Cicloalquilo" se refiere al sistema de anillos de carbón monocíclico no aromático saturado o no saturado de 3-8, más preferiblemente de 3-6 miembros por anillo, tales como el ciclopropil, ciclopentil, ciclohexil, y similares. En algunos casos, se especifica la opción del número de átomos de carbono en el cicloalquilo, por ejemplo, C_{1-3} cicloalquilo se refiere al cicloalquilo que tiene 1, 2 o 3 átomos de carbono. Un "cicloalquilo sustituido" es un cicloalquilo que es sustituido independientemente, a menos que se indique lo contrario, con uno o más, preferiblemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustitutos, como los aquí descritos, que se adhirieren a cualquier átomo disponible para proporcionar un compuesto estable. Se entiende que dichas sustituciones son químicamente factibles y enlazables con cualquier átomo disponible para suministrar un compuesto estable.

[0503] "Cicloalquilalquil" se refiere al un grupo -(alquileno)-cicloalquilo donde el alquileno aquí definido tiene especificado el número de átomos de carbono o si no se especifica tiene seis o menos, preferiblemente cuatro o menos átomos de carbono en la cadena principal; y cicloalquilo aquí definido tiene el número indicado de átomos de carbono. El C_{3-8}cicloalquiloalquilo tiene 3 a 8 anillos de átomos de carbono. El cicloalquiloalquilo ejemplar incluye, por ejemplo, ciclopropilmetileno, ciclobutiletileno, ciclobutilmetileno, y similares.

[0504] El término "alquileno" por sí mismo o como parte de otro sustituto significa una fracción lineal o ramificada de hidrocarbono saturado divalente derivado de un alcano que tiene el número del átomos de carbono indicados en el prefijo. Por ejemplo, (C_{1-6} significa uno a seis; C_{1-6} alquileno incluye metileno, etileno, propileno, 2-metilpropileno, pentileno, hexileno y similares). C_{1-4} alquileno incluye metileno -CH_2-, etileno -CH_2CH_2-, propileno -$CH_2CH_2CH_2$-, e isopropileno -$CH(CH_3)CH_2$- , -$CH_2CH(CH_3)$-, -CH_2-$(CH_2)_2CH_2$-, -CH_2-$CH(CH_3)CH_2$-, -CH_2-$C(CH_3)_2$-, -CH_2-$CH_2CH(CH_3)$- . Habitualmente, un grupo alquilo (o alquileno) tundra de 1 a 24 átomos de carbono, prefiriéndosi en la presente invención aquellos grupos que tiene 10 o menos, 8 o menos, o 6 o menos átomos de carbono. Cuando no se incluye un prefijo para indicar el número del átomos de carbono en una porción de alquileno, la fracción o porción de alquileno del mismo tendrá 12 o menos átomos de carbono en la cadena principal u 8 o menos átomos de carbono en la cadena principal, 6 o menos átomos de carbono en la cadena principal o 4 o menos átomos de carbono en la cadena principal.

[0505] “Aril” por sí mismo o como parte de otro sustituto se refiere a la porción de hidrocarbono poli insaturado monocíclico, bicíclico o policíclico que contiene 6 a 14 anillos de átomos de carbono. Los ejemplos sin limitación de los grupos ariles no sustituidos incluyen el fenil, 1-naftil, 2-naftil y 4-biel fenil. El grupo aril ejemplar, tal como el fenil o naftil, que pueden fusionarse opcionalmente con un cicloalquilo de preferiblemente 5-7, o más preferiblemente 5-6 miembros en el anillo.

[0506] "Arilalquilo" se refiere al -(alquileno)-aril, donde el grupo alquileno es el aquí definido y tiene indicado el número de átomos de carbono, o si no se

especifica que tiene seis o menos átomos de carbono en la cadena principal o cuatro o menos átomos de carbono en la cadena principal; y el aril es el aquí definido. Los ejemplos de arilalquilo incluyen bencil, fenetil, y similares.

[0507] Un "fenil sustituido" es un anillo fenil que es sustituido independientemente, a menos que se indique lo contrario, con uno o más, preferiblemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustitutos, como los aquí descritos, adheridos a cualquier átomo disponible para proporcionar un compuesto estable. Se entiende que dichas sustituciones son químicamente factibles y enlazables con cualquier átomo disponible para suministrar un compuesto estable.

[0508] "Heteroaril" por sí mismo o como parte de otro sustituto se refiere a la estructura del anillo aromático monocíclico contiene 5 o 6 átomos en el anillo, o un grupo aromático bicíclico que tiene 8 a 10 átomos, que contiene uno o más, preferiblemente 1-4, más preferiblemente 1-3, incluso más preferiblemente 1-2, heteroátomos independientemente seleccionados del grupo que consiste de O, S, y N. "heteroaril de 5 o 6 miembros" solo o en combinación se refiere a la monocíclico estructura de anillo aromático que contiene 5 o 6 átomos en el anillo, que contiene una o más, preferiblemente 1-4, más preferiblemente 1-3, incluso más preferiblemente 1-2, heteroátomos independientemente seleccionados del grupo que consiste de O, S, y N. Heteroaril también incluye S o N oxidizados , tal como sulfinil, sulfonil y N-óxido de un nitrógeno de anillo terciario. El átomo del carbono o nitrógeno es el punto de enlace de la estructura del anillo heteroaril para proporcionar un compuesto estable. Los ejemplos de los grupos heteroaril incluyen, pero no se limitan a, piridinil, piridazinil, pirazinil, indolizinil,

benzo[b]tienil, quinazolinil, purinil, indolil, quinolinil, pirimidinil, pirrolil, pirazolil, oxazolil, tiazolil, tienil, isoxazolil, oxatiadiazolil, isotiazolil, tetrazolil, imidazolil, triazolil, furanoil, benzdeluril, indolil, triazinil, quinoxalinil, cinnolinil, ftalaziniil, benzotriazinil, benzimidazolil, benzopirazolil, benzotriazolil, benzisoxazolil, isobenzdeluril, isoindolil, indolizinil, benzotriazinil, tienopiridinil, tienopirimidinal, pirazolopirimidinil, imidazopiridinas, benzotiaxolil, benzotienil, quinolil, isoquinolil, indazolil, pteridinil y tiadiazolil, y similares. Un "heteroaril sustituido" es un heteroaril que es sustituido independientemente, a menos que se indique lo contrario, con uno o más, preferiblemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustitutos, como los aquí descritos, adheridos a cualquier átomo disponible para proporcionar un compuesto estable. Se entiende que dichas sustituciones son químicamente factibles y enlazables con cualquier átomo disponible para suministrar un compuesto estable.

[0509] "Heteroarilalquilo" se refiere al -(alquileno)-heteroaril, donde el grupo alquileno es el aquí definido y tiene indicado el número de átomos de carbono, y si no se especifica tiene seis o menos átomos de carbono en la cadena principal o cuatro o menos átomos de carbono en la cadena principal; y el heteroaril es el aquí definido. Los ejemplos de heteroarilalquilo incluyen 2-piridilmetil, 2-tiazoliletil, y similares.

[0510] "Heterocicloalquilo" se refiere al grupo cicloalquilo aromático saturado o no saturado que contiene de uno a cinco heteroátomos seleccionados de N, O, y S, donde los átomos de nitrógeno y sulfuro se oxidizan opcionalmente, y el (los) átomo (s) de nitrógeno se cuaternizan opcionalmente, los átomos del anillo restante son C,

donde uno o dos Átomos C pueden ser reemplazados opcionalmente por carbonil. El heterocicloalquilo puede ser un sistema de anillos monocíclico, bicíclico o policíclico de 3 a 12, preferiblemente 4 a 10 átomos en el anillo, más preferiblemente 5 a 8 átomos en el anillo en el cual uno a cinco átomos en el anillo son heteroátomos seleccionados de –N=, -N-, -O-, -S-, -S(O)-, o $–S(O)_2$- y donde uno o dos átomos en el anillo se reemplazan opcionalmente por un grupo -C(O)-. El heterocicloalquilo también puede ser un anillo de alquilo heterocíclico fusionado con una anillo cicloalquilo, aril o heteroaril. Los ejemplos sin limitación de los grupos heterocicloalquilo incluyen pirrolidinil, piperidinil, imidazolidinil, pirazolidinil, fracciones de butirolactam, fracciones de valerolactam, fracciones de imidazolidinona, hidantoina, fracciones de dioxolano, ftalimida, fracciones de piperidina, fracciones de 1,4-dioxane, morfolinil, tiomorfolinil, tiomorfolinil-S-óxido, tiomorfolinil-S,S-óxido, piperazinil, piranil, fracciones de piridina, 3-pirrolinil, tiopiranil, fracciones de pirona , tetrahidrofurano, tetrahidrotioil fenil, quinuclidinil, y similares. Un grupo heterocicloalquilo puede adherirse al restante de la molécula a través del anillo de carbono o un heteroátomo.

[0511] "Heterocicloalquiloalquilo" se refiere al -(alquileno)-heterocicloalquilo, donde el grupo alquileno es el aquí definido y tiene indicado el número de átomos de carbono, y si no se especifica tiene seis o menos átomos de carbono en la cadena principal o cuatro o menos átomos de carbono en la cadena principal; y heterocicloalquilo es el aquí definido. Los ejemplos de heterocicloalquiloalquilo incluyen 2-piridilmetil, 2-tiazoliletil, y similares.

[0512] "Grupo protector" se refiere al grupo de átomos que Cuandosi adhieren a un grupo reactivo en una molécula enmascara, reduce o previene esa reactividad.

Los ejemplos de grupo protector pueden encontrarse en T.W. Greene y P.G. Wuts, PROTECTIVA GRUPOS IN ORGANIC CHEMISTRY, (Wiley, 4t ed. 2006), Beaucage & Iyer, *Tetrahedron* 48**:**2223-2311 (1992), y Harrison & Harrison *et al.*, COMPENDIUM DEL SYNTETIC ORGANIC METODS, Vols. 1-8 (John Wiley y Sons. 1971-1996). Un grupo protector de aminos representantivo incluye formil, acetil, triflúoroacetil, bencil, benciloxicarbonil (CBZ), *tert*-butoxicarbonil (Boc), trimetilsilil (TMS), 2-trimetilsilil-etanosulfonil (SES), tritil y grupos tritiles sustituidos , alliloxicarbonil, 9-fluoroenilmetiloxicarbonil (FMOC), nitro-veratriloxicarbonil (NVOC), tri-isopropilsilil (TIPS), fenilsulfonil y similares (ver también, Boile, A. L. (Editor), carbamatos, amidas, derivados de N-sulfonil, grupos de la fórmula-C(O)OR, donde R es, por ejemplo, metil, etil, t-butil, bencil, feniletil, CH_2=$CHCH_2$-, y similares, grupos de la fórmula-C(O)R', donde R' es, por ejemplo, metil, fenil, triflúorometil, y similares, grupos de la fórmula-SO_2R", donde R" es, por ejemplo, tolil, fenil, triflúorometil, 2,2,5,7,8-pentametilcroman-6-il, 2,3,6-trimetil-4-metoxilfenil, y similares, y silanil que contiene grupos, tal como 2-trimetilsililetoximetil, t-butildimetilsilil, triisopropilsilil, y similares, CURRENT PROTOCOLS IN NUCLEIC ACID CHEMESTRY, John Wiley y Sons, New York,Volume 1, 2048). El grupo protector hidroxil representantivo incluye, pero no se limita a, acetil, benzoil,dimetoxitritil, metoxietioximetil, metoximetil, p-metoxibencil, tetrahidropiranil, metiltiometil, tritil, t-butildimetilsililoximetil y trialquilosilil, tal como TMS, TIPS y similares.

[0513] Tal como se usa aquí, "Grupo saliente" o "Grupo Lábil" tiene el significado asociado convencionalmente en la química orgánica sintética, es decir, un átomo o grupo capaz de ser desplazado por un nucleófilo e incluye halos (tal

como cloro, bromo, y yodo), alkanosulfoniloxi, arenesulfoniloxi, alquilocarboniloxi (acetoxi), aril carboniloxi, mesiloxi, tosiloxi, triflúorometanosulfoniloxi, ariloxi (2,4-dinitrofenoxi), metoxi, N,O-dimetilhidroxilamino, y similares.

[0514] "Tautómeros" significa un compuesto producido por un fenómeno donde un protón de un átomo de la molécula cambia a otro átomo. Ver, Jerry March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structures*, Fourth Edition, John Wiley & Sons, pages 69-74 (1992). Los tautómeros también se refieren a uno de dos o más isómeros estructurales que existen en equilibrio y que se convierten fácilmente de una forma isomérica a otra. Los ejemplos de tautómeros incluyen tautómeros ceto-enol, tal como acetona/propen-2-ol, imina-enamina y similares, tautómeros de cadena de anillos, como glucosa/2,3,4,5,6-pentahidroxi-hexanal y similares, formas tautoméricas del grupo heteroaril que contiene configuración de átomo de anillo -N=C(H)-NH-, tal como pirazoles, imidazoles, benzimidazoles, triazoles, y tetrazoles. Cuando el compuesto contiene, por ejemplo, un grupo ceto u oxime o fracciones aromáticas, puede ocurrir alguno isomerismo tautomérico (‘Tautomerismo). Los compuestos aquí descritos pueden tener uno o más tautómeros y por lo tanto incluyen varios isómeros. Una persona con destreza común en el arte reconocería que son posibles otras configuraciones tautomérica de átomos del anillo. Todas las formas isoméricas de estos compuestos se incluyen expresamente en la presente invención.

[0515] Ciertos compuestos de la presente invención pueden existir en formas no solvatadas así como en formas solvatadas, incluyendo formas hidratadas. "Hidrato" se refiere al complejo formado por la combinación de moléculas de agua con moléculas o iones del soluto. "Solvato" se refiere al complejo formado por la

combinación de moléculas solventes con moléculas o iones del soluto. El solvente puede ser un compuesto orgánico, un compuesto inorgánico, o ambos. El solvato incluye el hidrato. Algunos ejemplos de solventes incluyen, pero no se limitan a, metanol, N,N-dimetilformamida, tetrahidrofurano, dimetilsulfóxido, y agua. En general, las formas solvatadas son equivalentes a las formas no solvatadas y se incluyen en el alcance de la presente invención. Ciertos compuestos de la presente invención pueden existir en múltiples formas cristalinas o amorfas. En general, todas las formas físicas son equivalentes para los usos contemplados por la presente invención y se encuentran dentro del alcance de la presente invención

[0516] Tal como se usa aquí, el término " enfermedad o condición relacionada con Fms y Kit" se refiere a la enfermedad o condición en la cual la función biológica de la proteína quinasa Fms, incluyendo cualquier mutación de la misma, una proteína quinasa Kit, incluyendo cualquier mutación de la misma, o ambas proteínas quinasa Fms y Kit, incluyendo cualquier mutación de éstas, afectan el desarrollo, curso, y/o síntomas de dicha enfermedad o condición, y/o en la cual la modulación de la proteína quiniasa Fms y/o Kit altera el desarrollo, curso, y/o síntomas de la enfermedad o condición. Una enfermedad o condición relacionada con Fms y/o Kit incluye una enfermedad o condición para la cual la modulación brind un beneficio terapéutico, es decir, donde el tratamiento con un inhibidor de proteína quinasa Fms y/o Kit, preferiblemente un inhibidor dual de Fms/Kit, incluyendo uno o más compuesto(s) aquí descritos, provee un beneficio terapéutico al sujeto que sufre de o está en riesgo por dicha enfermedad o condición.

[0517] Tal como se usa aquí, el término "enfermedad o condición relacionada con Fms" y similares se refiere a la enfermedad o condición en la cual la función

biológica de la proteína quinasa Fms, incluyendo cualquier mutación de la misma, afecta el desarrollo, curso, y/o síntomas de dicha enfermedad o condición, y/o en la cual la modulación de la proteína quinasa Fms altera el desarrollo, curso, y/o síntomas de la enfermedad o condición. Una enfermedad o condición relacionada con Fms incluye una enfermedad o condición para la cual la modulación brinda un beneficio terapéutico, es decir, donde el tratamiento con un inhibidor de proteína quinasa Fms, preferiblemente un inhibidor selectivo de Fms, incluyendo uno o más compuesto(s) aquí descritos, provee un beneficio terapéutico al sujeto que sufre de o está en riesgo por dicha enfermedad o condición.

[0518] Tal como se usa aquí, el término "enfermedad o condición relacionada con Kit" y similares se refiere a la enfermedad o condición en la cual la función biológica de la proteína quinasa Kit, incluyendo cualquier mutación de la misma, afecta el desarrollo, curso, y/o síntomas de dicha enfermedad o condición, y/o en la cual la modulación de la proteína quinasa Kit altera el desarrollo, curso, y/o síntomas de la enfermedad o condición. Una enfermedad o condición relacionada con Kit incluye una enfermedad o condición para la cual la modulación brinda un beneficio terapéutico, es decir, donde el tratamiento con un inhibidor de proteína quinasa Kit, incluyendo uno o más compuesto(s) aquí descritos, provee un beneficio terapéutico al sujeto que sufre de o está en riesgo por dicha enfermedad o condición.

[0519] Tal como se usa aquí, el término "inhibidor dual de Fms/Kit " se refiere a un compuesto que inhíbe las proteínas quinasa Fms y Kit , es decir un compuesto que tiene un CI_{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 determinado en un

ensayo generalmente aceptado de la actividad de Quinasa Fms y que tiene un CI_{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 determinado en un ensayo generalmente comparable de la actividad de la quinasa Kit, donde la actividad no es aproximadamente equipotente en cada una. Los compuestos se consideran aproximadamente equipotentes si el coeficiente del CI_{50} de la actividad de la quinasa Kit dividido por el CI_{50} de la Quinasa Fms está en el rango de 20 a 0.05, también 10 a 0.1, también 5 a 0.2. Tales compuestos son efectivos al tratar una enfermedad o condición que esté relacionada con la Fms y Kit. Tales compuestos son preferiblemente, pero no necesariamente, selectivos con respecto a otras proteínas quinasas, es decir, cuando se comparan con otra proteína quinasa, el CI_{50} por la otra quinasa dividido por el CI_{50} por la quinasa Raf >10, también >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. Preferiblemente, los compuestos son selectivos con relación a otras proteínas quinasas incluyendo, pero no limitado a CSK, quinasa receptora de insulina, AMPK, PDGFR o VEGFR. Mientras se entiende que puede usarse un inhibidor dual de la Fms/Kit para tratar cualquier enfermedad o condición relacionada con la Fms, la inhibición dual de la Fms y Kit brinde efectos beneficiosos al tratar ciertas enfermedades o condiciones, incluyendo, per no limitadas a, cáncer de seno, cáncer de próstata , mieloma múltiple, melanoma, leucemia mieloide aguda, glioblastoma, metástatis cerebral, neurofibromatosis, tumores estromales gastrointestinales, artritis reumatoide, o esclerosis múltiple.

[0520] Tal como se usa aquí, el término “inhibidor dual Fms/Flt-3” se refiere al un compuesto que inhíbe la actividad de las proteínas quinasa Fms y Flt-3, es decir un

compuesto que tiene un CI_{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 determinado en un ensayo generalmente aceptado de la actividad de la Quinasa Fms y que tiene un CI_{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 determinado en un ensayo generalmente comparable de la actividad de la quinasa Flt-3, donde la actividad no es aproximadamente equipotente en cada una. Los compuestos se consideran aproximadamente equipotentes si el coeficiente del CI_{50} de la actividad de la quinasa Flt-3 dividido por el CI_{50} de la actividad de la quinasa Fms está en el rango de 20 a 0.05, también 10 a 0.1, también 5 a 0.2. Tales compuestos son preferiblemente, pero no necesariamente, selectivos con respecto a otras proteínas quinasas, es decir, cuando se comparan con otra proteína quinasa, el CI_{50} por la otra quinasa dividido por el CI_{50} por la quinasa Raf >10, también >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. Preferiblemente, los compuestos son selectivos con relación a otras proteínas quinasas incluyendo, pero no limitado a CSK, quinasa receptora de insulina, AMPK, PDGFR o VEGFR. Mientras se entiende que puede usarse un inhibidor dual de Fms/Flt-3 para tratar cualquier enfermedad o condición relacionada con la Fms, laa inhibición dual de la Fms y Flt-3 brinda efectos beneficiosos al tratar ciertas enfermedades o condiciones, incluyendo, pero no limitadas a, cáncer de seno, cáncer de próstata , mieloma múltiple, melanoma, leucemia mieloide aguda, glioblastoma, metástatis cerebral, neurofibromatosis, tumores estromales gastrointestinales, artritis reumatoide, o esclerosis múltiple.

[0521] Tal como se usa aquí, El término “inhibidor dual de Fms/Trk” se refiere al compuesto que inhibe las proteínas quinasa Fms y Trk , es decir un compuesto que tiene un CI_{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 determinado en un ensayo generalmente aceptado de Actividad de la quinasa Fms que tiene un CI_{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 determinado en un ensayo generalmente comparable de la actividad de la quinasa Trk (es decir alguna o más de TrkA, TrkB y TrkC), donde la actividad no es aproximadamente equipotente en cada una. Los compuestos se consideran aproximadamente equipotentes si el coeficiente del CI_{50} de la actividad de la quinasa Trk (es decir al menos una de las TrkA, TrkB y TrkC) dividido por el CI_{50} de la actividad de la quinasa Fms está en el rango de 20 a 0.05, también 10 a 0.1, también 5 a 0.2. Dichos compuestos son efectivos al tratar una enfermedad o condición relacionada con la Fms y Trk. Tales compuestos son preferiblemente, pero no necesariamente, selectivos con respecto a otras proteínas quinasas, es decir, cuando se comparan con otra proteína quinasa, el CI_{50} por la otra quinasa dividido por el CI_{50} por la quinasa Raf >10, también >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. Preferiblemente, los compuestos son selectivos con relación a otras proteínas quinasas incluyendo, pero no limitado a CSK, quinasa receptora de insulina, AMPK, PDGFR o VEGFR. Mientras se entiende que puede usarse un inhibidor dual de Fms/Trk para tratar cualquier enfermedad o condición relacionada con la Fms, la inhibición dual de la Fms y Trk brinda efectos beneficiosos al tratar ciertas enfermedades o condiciones, incluyendo, pero no limitadas a, cáncer de seno, cáncer de próstata , mieloma múltiple, melanoma, leucemia mieloide aguda,

gliobastoma, metástasis cerebral, neurofibromatosis, tumores estromales gastrointestinales, artritis reumatoide, o esclerosis múltiple.

[0522] Tal como se usa aquí, el término “inhibidor selectivo de la Fms” se refiere al compuesto que inhibe selectivamente la Quinasa Fms relativa a la quinasa Kit, es decir un compuesto que tiene un CI_{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 as determinado en un ensayo generalmente aceptado de la actividad de la quinasa Fms y cuando se determina en un ensayo generalmente comparable la actividad de la quinasa Kit tendrá un coeficiente de CI_{50} de la quinasa Kit dividido por el CI_{50} de la Quinasa Fms de >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. Dichos compuestos son efectivos al tratar una enfermedad o condición mediada por la proteína quinasa Fms sin afectar la proteína quinasa Kit. Dichos compuestos son efectivos al tratar una enfermedad o condición relacionada con la Fms. Tales compuestos son preferiblemente, pero no necesariamente, selectivos con respecto a otras proteínas quinasas, es decir, cuando se comparan con otra proteína quinasa, el CI_{50} por la otra quinasa dividido por el CI_{50} por la quinasa Raf >10, también >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. Preferiblemente, los compuestos son selectivos con relación a otras proteínas quinasas incluyendo, pero no limitado a CSK, quinasa receptora de insulina, AMPK, PDGFR o VEGFR. Mientras se entiende que puede usarse un inhibidor de la Fms para tratar cualquier enfermedad o condición relacionada con la Fms, la selectividad de la Fms brinda efectos beneficiosos al tratar ciertas enfermedades o condiciones, incluyendo, pero no limitadas a esclerosis

múltiple, Enfermedad de Alzheimer, Enfermedad de Parkinson, isquemia global, artritis reumatoide, osteoartritis, osteoporosis, peri-osteolisis prostética, glomerulonefritis, nefritis intersticial, Nefritis lúpica, nefropatía diabética, o Hipertrofia renal.

[0523] Tal como se usa aquí, el término "barrera sangre-cerebro" se refiere a la barrera física en el sistema circulatorio que evita que muchas sustancias, incluyendo ciertos fármacos con pequeñas moléculas, entren al sistema nervioso central (SNC). Los fármacos previstos para interactuar con objetivos moleculares en el SNC deben cruzar la barrera sangre-cerebro para alcanzar sus objetivos previstos. Inversamente, los agentes que actúan periféricamente no deberían cruzar la barrera sangre-cerebro para evitar efectos adversos del SNC. La capacidad de un compuesto de penetrar la barrera sangre-cerebro se expresa como la permeabilidad de la barrera sangre-cerebro o el coeficiente de las concentraciones en estado estable del compuesto en el cerebro y en la sangre. La permeabilidad experimental de la barrera sangre-cerebro puede medirse mediante métodos *in vivo*. Pueden usarse varios métodos para medir la fracción del compuesto transportado desde la sangre hasta el tejido cerebral, incluyendo el fraccionamiento de la sangre del cerebro, perfusión cerebral, índice de consumo del cerebro y microdiálisis intracerebral. Sin embargo, estos métodos *in vivo* son laboriosos y de bajo rendimiento. En la práctica, los métodos computacionales *in silico* se usan frecuentemente para predecir la permeabilidad de la barrera sangre-cerebro antes de la confirmación *in vivo*. La mayoría de los modelos de la barrera sangre-cerebro que han sido construidos hasta ahora, se basan en la asunción de que la mayoría de los compuestos son transportados a través de la barrera sangre-cerebro por difusión pasiva. De todas las propiedades fisicoquímicas,

el área de la superficie polar (PSA) muestra la mejor correlación con la permeabilidad de la barrera sangre-cerebro para compuestos difundidos pasivamente. La evidencia empírica sugiere que los compuestos que tiene un área de superficie polar de 100 o más generalmente tienen una baja probabilidad de cruzar la barrera sangre-cerebro. El área de superficie polar se calcula fácilmente a partir de la estructura del compuesto usando un algoritmos publicado (Ertl et al., J. Med. Chem. 2048, 43:3714-3717). Mientras se entiende que un inhibidor selectivo de la Fms puede usarse para tratar cualquier enfermedad o condición relacionada con la Fms, los compuestos que cruzan efectivamente la barrera sangre-cerebro brindan efectos beneficiosos al tratar ciertas enfermedades o condiciones, incluyendo, pero no limitadas a, esclerosis múltiple, Enfermedad de Alzheimer, Enfermedad de Parkinson, e isquemia global, mientras que los compuestos que no cruzan efectivamente la barrera sangre-cerebro brindan efectos beneficiosos al tratar ciertas enfermedades o condiciones, incluyendo, pero no limitadas a, artritis reumatoide, osteoartritis, osteoporosis, peri-osteolisis prostética, glomerulonefritis, nefritis intersticial, Nefritis lúpica, nefropatía diabética, o Hipertrofia renal.

[0524] Como se usa aquí, los términos “tratar”, “que trata”, “terapia”, “terapias”, y términos similares se refieren a la administración del material, por ejemplo, uno o más de los compuestos aquí descritos en una cantidad efectiva para prevenir, aliviar o mejorar uno o más síntomas de un enfermedad o condición, es decir, indicación, y/o prolongar la supervivencia del sujeto bajo tratamiento.

[0525] Como se usa aquí, los términos “tratar”, “que trata”, “terapia”, “terapias”, y términos similares se refieren a la administración del material, por ejemplo, uno o más de los compuestos aquí descritos en una cantidad efectiva para prevenir, aliviar

o mejorar uno o más síntomas de un enfermedad o condición, es decir, indicación, y/o prolongar la supervivencia del sujeto bajo tratamiento.

[0526] Como se usa aquí, el término "forma sólida" se refiere a una Preparación de sólida (es decir, una Preparación de que no es gas ni líquido) de un compuesto farmacéuticamente activo que es apropiado para la administración de un sujeto animal para finas terapéuticos. La forma sólida incluye cualquier complejo, tal como 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 usarse en la Preparación de de una composición apropiada que tenga propiedades farmacéuticas mejoradas. Por ejemplo, la forma sólida puede usarse en una formulación que comprenda al menos un portador o excipiente farmacéuticamente aceptable.

[0527] Como se usa aquí, el término material "sustancialmente cristalino" comprende el material que tiene más del 90% de cristalinidad, y el material "cristalino" comprende el material que tiene aproximadamente 98% de cristalinidad.

[0528] Como se usa aquí, el término material "sustancialmente amorfo" comprende el material que no tiene más de aproximadamente 10% de cristalinidad y material "amorfo" comprende el material que no tiene más de aproximadamente el 2% de cristalinidad.

[0529] Como se usa aquí, el término material "semi-cristalino" comprende el material que tiene más del 10% de cristalinidad, pero no más del 90% de

cristalinidad; preferiblemente material “semi-cristalino” comprende el material que tiene más de un 20% de cristalinidad pero no más del 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 proveer una forma sólida “semi-cristalina” forma sólida. Dicha forma sólida “semi-cristalina” puede prepararse mediante métodos conocidos en el arte, por ejemplo al mezclar una forma sólida amorfa con una forma sólida cristalina en el coeficiente deseado. En algunos casos, puede prepararse un compuesto mezclado con ácido o base forma un complejo amorfo; un solido semi-cristalino puede prepararse al usar una cantidad de un componente compuesto en exceso de la estequiometria del compuesto y ácido o base en el complejo amorfo, resultando así en una cantidad de complejo amorfo que se basa en la estequiometria del mismo, con compuesto en exceso de una forma cristalina. La cantidad de compuesto en exceso usado en la Preparación de complejo puede ajustarse para brindar el coeficiente deseado de complejo amorfo al complejo cristalino en la mezcla resultante de las formas sólidas. Por ejemplo, cuando el complejo amorfo del ácido o base y el compuesto tienen una estequiometria 1: 1, preparando dicho complejo con una proporción molar 2:1 del compuesto para el ácido o base resultará en una forma sólida con 50% de complejo amorfo y 50% de compuesto cristalino. Dicha mezcla de formas sólidas puede ser beneficiosa como un producto farmacéutico, por ejemplo, al proporcionar un componente amorfo que tenga propiedades biofarmacéuticas mejoradas junto con el componente cristalino. El componente amorfo puede estar más fácilmente biodisponible mientras que el componente cristalino podría tener una biodisponibilidad retardada. Dicha mezcla puede brindar una exposición rápida y extendida al compuesto activo.

[0530] Como se usa aquí, el término “complejo” se refiere a una combinación de un compuesto farmacéuticamente activo y una especia molecular adicional que forma o produce una nueva especie química en forma sólida. En algunos casos, el complejo puede ser una sal, es decir, cuando la especie molecular adicional proporciona un contracción ácido/base a un grupo ácido/base del compuesto resultando en una interacción ácido: base que forma una sal típica. Mientras que dichas formas salinas son generalmente cristalinas, también pueden ser parcialmente cristalinas, sustancialmente amorfas, o formas 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 mediante la forma de una interacción típica ácido: base, pero aún así forman una estructura sustancialmente cristalina. Los co cristales también se forman a partir de una sal del compuesto y una especia molecular adicional. En algunos casos, el complejo es un complejo sustancialmente amorfo, el cual puede contener sales similares a interacciones ácido: base que no forma cristales de sal típicos, pero en su lugar forman un sólido sustancialmente amorfo, es decir, un sólido cuando patrón de difracción de rayos X no muestra picos agudos (es decir, muestra un halo amorfo).

[0531] Como se usa aquí, el término “estequiometria” se refiere a la proporción molar de una combinación de dos o más componentes, por ejemplo, la relación molar del ácido o base para el compuesto que forma un complejo amorfo. Por ejemplo, una mezcla de ácido o base 1:1 con un compuesA (es decir, 1 mol ácida o base por mol de compuesto) que resulta en una forma sólida amorfa tiene una estequiometria 1:1.

[0532] Como se usa aquí, el término “composición” se refiere a una Preparación de farmacéutica apropiada para la administración a un sujeto para finas terapéuticos que contiene al menos un compuesto farmacéuticamente activo, incluyendo cualquier forma sólida del mismo. La composición puede incluir al menos un componente farmacéuticamente aceptable para proveer una formulación mejorada del compuesto, tal como un portador o excipiente apropiado.

[0533] El término “farmacéuticamente aceptables” indica que el material indicado no tiene propiedades que puedan causar que un prácticamente médico razonablemente prudente evite la administración del material al paciente, teniendo en consideración la enfermedad o condición que será tratada y la respectiva vía de administración. Por ejemplo, se requiere comúnmente que dicho material sea esencialmente estéril, por ejemplo, para iniectables.

[0534] En el presente contexto**,** el término “terapéuticamente efectivo” o "cantidad efectiva" indica que los materiales o la cantidad de material es efectiva para prevenir, aliviar o mejorar uno o más síntomas de la enfermedad o condición médica, y/o prolongar la supervivencia del sujeto bajo tratamiento.

[0535] "Forma de dosis unitaria " se refiere a la composición prevista para un administración única para tratar un sujeto que sufre de una enfermedad o condición médica. Cada forma de dosis unitaria comprende cada ingrediente activo de esta invención más los excipientes farmaceúticamente aceptable. Los ejemplos de formas de dosis unitaria son tabletas individuales, cápsulas individuales, polvos a granel, soluciones líquidas, ungüentos, cremas, gotas oculares, supositorios, emulsiones o suspensiones. El tratamiento de la enfermedad o condición puede requerir la administración periódica de las formas de dosis unitaria, por ejemplo: una

forma de dosis unitaria dos o más veces al día, una con cada comida, una cada cuatro horas u otro intervalo, o solo una por día. La expresión "forma de dosis unitaria oral " indica una forma de dosis unitaria que debe tomarse oralmente.

[0536] En el presente contexto, el término “sinérgicamente efectivo” o “efecto sinérgico” indica que dos o más compuestos que son terapéuticamente efectivos, cuando se usan en combinación, brindan efectos terapéuticos mejorados mayores al efecto aditivo que podría esperarse con base en el efecto de cada compuesto usado en sí.

[0537] En el contexto de los compuestos que se unen a un objetivo, los términos “mayor afinidad” e “indicaciones selectivas” indica que el compuesto se une más fuertemente que el compuesto de referencia, o que el mismo compuesto es una condición de referencia, *es decir*, con una menor constante de disociación. En algunas formas de realización, la mayor afinidad es de al menos 2, 3, 4, 5, 8, 10, 50, 100, 200, 400, 500, 1000, o 10,000 veces la mayor afinidad.

[0538] Tal como se usa aquí en relación con los compuestos de la invención, el término “sintetizante” y los términos similares significan la síntesis química de uno o más materiales precursores.

[0539] “Ensayo” significa la creación de las condiciones experimentales que reúnen los datos de un resultado particular de la exposición a condiciones experimentales específicas. Por ejemplo, las enzimas pueden ser ensayadas con base en su habilidad para actuar sobre el sustrato detectable. Un compuesto puede ser ensayado con base en su capacidad de unirse a una molécula o moléculas con objetivo particular.

[0540] Como se usa aquí, el término “modulación” o “modular” se refiere a un efecto de alteración de la actividad biológica (es decir, aumento o reducción de la actividad), especialmente un actividad biológica asociada con una biomolécula particular tal como proteína quinasa. Por ejemplo, un inhibidor de un biomolécula particular modula la actividad de esta biomolécula, por ejemplo, una enzima, al disminuir la actividad de la biomolécula, tal como una enzima. Dicha actividad se índica típicamente en términos de una concentración inhibitoria (CI_{50}) del compuesto por un inhibidor con respecto a una enzima, por ejemplo.

[0541] En el contexto de uso, la prueba o examen de los compuestos que son o pueden ser moduladores, el término “contacto” significa los compuestos que están en proximidad suficiente a una molécula, complejo, célula, tejido, organismo particular u otro material especificado para que ocurren interacciones potenciales de unión y/o reacciónes químicas entre el compuesto y otros materiales especificados.

[0542] “Dolor” o “condición de dolor” puede ser dolor agudo y/o crónico, incluyendo, sin limitación, sin limitación, aracnoiditis; artritis (por ejemplo, osteoartritis, artritis reumatoide, espondilitis no anquilosante, gota); dolor de espalda (por ejemplo, ciática, ruptura de disco, espondilolistesis, radiculopatía); dolor de quemadura; dolor de cáncer; dismenorrea; dolor de cabeza (por ejemplo, migraña, cefalea en racimos, tensión dolor de cabeza); dolor de cabeza y facial (por ejemplo, neuralgia craneal, neuralgia trigeminal); hiperalgesia; hiperpatía; dolor inflamatorio (por ejemplo, dolor asociado con síndrome de intestino irritable, colitis ulcerativa, enfermedad de Crohn, cistitis, dolor por infección bacteriana, fungal o viral; formación de tejido queloide o escara, dolor de parto o labor de parto, dolor muscular (por ejemplo, como resultado de polimiositis, dermátomoiositis, miositis

por cuerpos de inclusión, lesión por estrés repetitivo (por ejemplo, calambre en las manos, síndrome de túnel del carpio, tendinitis, tenosinovitis)); síndromes de dolor miofascial (por ejemplo, fibromialgia); dolor neuropático (por ejemplo, neuropatía diabética, causalgia, neuropatía por atrapamiento, avulsión plexo braquial, neuralgia occipital, gota, síndrome de distrofia simpatética de reflejo, dolor de miembro fantasma o post-amputación, neuralgia posherpética, síndrome de dolor central, o dolor de nervios que resulta de un trauma (por ejemplo, lesión de nervios), enfermedad (por ejemplo, diabetes, esclerosis múltiple, síndrome de Guillan-Barre, miastenia gravis, enfermedades neurodegenerativas como enfermedad de Enfermedad de Parkinson, Enfermedad de Alzheimer, esclerosis lateral amiotrófica, o tratamiento de cáncer); dolor asociado con afecciones de la piel (por ejemplo, culebrilla, herpes simplex, tumores de la piel, quistes, neurofibromatosis); lesiones deportivas (por ejemplo, cortes, esguinces, estrías, quemaduras, dislocaciones, fracturas, médula espinal, cabeza); estenosis espinal; dolor quirúrgico, anodinia táctil; afecciones temporomandibulares; enfermedad o lesión vascular (por ejemplo, vasculitis, enfermedad de la arteria coronaria, lesión por reperfusión (por ejemplo, después de isquemia, ataques o infartos de miocardio)); dolor de otros órganos o tejidos específicos (por ejemplo, dolor ocular, dolor corneal, dolor de huesos, dolor de corazón, dolor visceral (por ejemplo, riñón, vesícula biliar, gastrointestinal), dolor de articulaciones, dolor dental, hipersensibilidad pélvica, dolor pélvico, cólico renal, incontinencia urinaria); otros dolores asociados con enfermedades (por ejemplo, anemia de células falciformes, SIDA, herpes zoster, psoriasis, endometriosis, asma, enfermedad pulmonar obstructiva crónica (EPOC), silicosis, sarcoidosis pulmonar, esofagitis, acidez gástrica, afección de reflujo gastroesofageal, ulceras estomacales y duodenales, dispepsia funcional, enfermedad de reabsorción

ósea, osteoporosis, malaria cerebral, meningitis bacteriana); o dolor debido a injerto vs. huésped o rechazo de aloinjertos.

Objetivos de la quinasa e indicaciones de la invención

[0543] Las proteínas quinasas juegan papeles clave en la propagación de las señales bioquímicas en diversas vías biológicas. Se han descrito más de 500 quinasas, y las quinasas específicas han estado implicadas en un amplio rango de enfermedades o condiciones (es decir, indicaciones), incluyendo por ejemplo sin limitación, cáncer, enfermedad cardiovascular, enfermedad inflamatoria, enfermedad neurológica, y otras enfermedades. Como tal, las quinasas representan puntos de control importantes para la intervención terapéutica de pequeñas moléculas. Las proteínas quinasas con objetivo específico contemplados por la presente invención se describen en el arte, incluyendo, sin limitación, proteínas quinasas como se describe en la Aplicación de la Patente de U.S. Serial No. 11/473,347 (ver también, publicación PCT WO2007002433), la divulgación de las cuales se incorpora a la presente por referencia ya que se relaciona como tal a los objetivos de la quinasa, así como lo siguiente:

[0544] **Fms:** **Quinasa Objetivo** Fms (es decir, Sarcoma felino de McDonough) es un miembro de la familia de genes aislados originalmente a partir de la cepa Susan McDonough de virus del sarcoma felino. La Fms es una tirosina quinasa de tipo transmembrana de 108.0 kDa codificada por el cromosoma 5q33.2-q33.3 (símbolo: CSF1R). La estructura de la Fms receptora de tipo transmembrana comprende dos dominios similares a la inmunoglobina, un dominio similar al a IgC2, dos dominios adicionales similares a la inmunoglobina y un dominio TK.

[0545] La Fms es la receptora del factor estimulante de colonias de macrófagos (M-CSF), y es crucial para el crecimiento y diferenciación del linaje monocito-macrófago Al unirse la M-CSF al dominio extracelular de la Fms, el receptor dimeriza y fosforaliza automáticamente los residuos citoplásmicos de la tirosina.

[0546] La M-CSF, fue descrita por primera vez por Robinson y asociados (Blood. 1969, 33:396-9), como una citoquina que controla la producción, diferenciación y función de los macrófagos. La M-CSF estimula la diferenciación de las células para madurar los monocitos y prolonga la supervivencia de éstos. Además la M-CSF mejora la citotoxicidad, la producción de superóxido, la fagocitosis, quimotaxis, y la producción de factores adicionales en la citoquina secundaria en los monocitos y macrófagos. Los ejemplos de dichos factores adicionales incluyen el factor de estimulación de colonias de granulocitos (G-CSF), interleuquina-6 (IL-6), y interleuquina-8 (IL-8). La M-CSF estimula la hematopoyesis, promueve la diferenciación y proliferación de las células progenitoras osteoclásticas y tiene un profundo efecto en el metabolismo de los lípidos. Además, la M-CSF es importante en el embarazo. Fisiológicamente, se producen grandes cantidades de M-CSF en la placenta, y se cree que la M-CSF juega un papel esencial en la diferenciación de trofoblástos (Motoyoshi, Int J Hematol. 1998, 67:109-22). Los niveles elevados de la M-CSF en suero en el embarazo temprano pueden participar en los mecanismos inmunológicos responsables por el mantenimiento del embarazo (Flanagan & Lader, Curr Open hematol. 1998, 5:181-5).

[0547] La expresión aberrante y/o activación de la Fms ha estado implicada en la leucemia mieloide aguda, AML (Ridge et al, Proc. Nat. Acad. Sci., 1990, 87:1377-

1380). Se cree que las mutaciones en el codón 301 producen la transformación neoplásica mediante la independencia del ligando y la actividad constitutiva de la tirosina quinasa en el receptor. El residuo de la tirosina en el codón 969 ha mostrado estar involucrada en una actividad regulatoria negativa, la cual es interrumpida por las sustituciones de los aminoácidos. Por consiguiente, las mutaciones de la Fms son más prevalentes (20%) en la leucemia mielomonocítica crónica y AML tipo M4 (23%), ambas de las cuales se caracterizan por la diferenciación monocítica.

[0548] Una condición relacionada con la AML es la leucemia mieloide crónica (LMC). Durante la crisis blástica mieloide (CB) de la LMC, ocurren anormalidades adicionales no aleatorias en 80% de los pacientes. Sin embargo, se han reportado que estos cambios citogénicos preceden los signos clínicos de LMC-BC por varios meses a años que sugieren que otros eventos biológicos pueden participar en los procesos de varios pasos de la transformación aguda de la LMC. La producción autocrina de los factores de crecimiento ocurre en varias afecciones malignas hematológicas y particularmente en la AML. Specchia et al [Br J Haematol. 1992 Mar; 80(3):310-6] han demostrado que el gen beta IL-1 se expresa en la mayoría de los casos de LMC en la crisis blástica mieloide, y que una alta proporción de casos mostraron expresión constitutiva del gen M-CSF. Muchos de los mismos pacientes en el estudio de Specchia et al demostraron co-expresión simultánea de la Fms. Después de la exposición de las células leucémicas al acetato de miristato forbol (AMF), se documentó la liberación de la proteína M-CSF en tres de cinco pacientes estudiados; sin embargo, no se detectó interleuquina 3 (IL-3), factor de estimulación de colonias de granulocitos (G-CSF) significativo en dichos pacientes. Esto demuestra los distintos patrones de secreción de factores de crecimiento que existen

en la AML y LMC, y que probablemente los distintos eventos moleculares se involucran en la proliferación de la leucemia.

[0549] La observación de que la producción de M-CSF, el principal factor de crecimiento de macrófagos, aumenta en los tejidos durante la inflamación (Le Meur et al, J. Leukocite Biology. 2002;72:530-537) proporciona un papel de la Fms en ciertas enfermedades. Por Ejemplo, la EPOC se caracteriza por la limitación del flujo de aire que no es completamente reversible. La limitación del flujo de aire es usualmente progresiva y está asociada con una respuesta inflamatoria anormal de los pulmones a las partículas o gases nocivos. La inflamación crónica de la EPOC se observa a través de las vías aéreas, parénquima y vasculatura pulomonar. La población de las células inflamatorias consiste de neutrófilos, macrófagos y linfocitos T junto con eosinófilos en algunos pacientes. Los macrófagos juegan un papel orquestante en la inflamación de la EPOC al liberar mediadores como TNF-a, IL-8 y LTB4, los cuales pueden dañar las estructuras del pulmón y/o mantener la inflamación neutrofílica.

[0550] Además, las señales de la M-CSF/fms son críticas para la formación osteoclástica y la supervivencia de los precursores osteoclásticos. Por ejemplo, la pérdida de estrógenos en la menopausia resulta en el aumento de M-CSF y por lo tanto el aumento del número de osteoclastos y la reabsorción ósea que produce un alto riesgo de fractura y osteoporosis. Consiguientemente, el blotato de esta señal es un objetivo para la inhibición de la reabsorción ósea (Teitelbaum, Science. 2000;289:1504; Rohan, Science. 2000;289:1508).

[0551] La Arterioesclerosis, una enfermedad inflamatoria de las paredes de las venas, está asociada con morbidez y mortalidad significativas. Un efecto beneficioso de la inhibición de la Fms inhibición en el tratamiento y la prevención de la arterioesclerosis depende de varias observaciones (Libby, Nature. 2002;420:868-874). Primero , los monocitos residentes en la arteria íntima aumentan la expresión de los receptores depuradores e internalizan las lipoproteínas modificadas. Los macrófagos Los macrófagos llenos de lípidos resultantes se desarrollan en células espumosas características de la lesión arteroesclerótica. Los macrófagos en la ateroma secretan citoquinas y factores de crecimiento involucrados en la progresión de la lesión. Adicionalmente, los macrófagos se duplican dentro de la íntima. A través de la Fms, la M-CSF activa la transición desde los monocitos hasta los macrófagos llenos de lípidos y aumentan la expresión del receptor depurador A. De hecho, las places arterioescleróticas sobre expresan la M-CSF lo cual es crítico para la progresión artrioesclerótica. Se ha encontrado que los ratones deficientes en M-CSF experimentan arterioesclerosis menos severa que los ratones con M-CSF normal (Rajavashist, et. al., J. Clin. Invest. 1998;101:2702-2710; Qiao, et. al., Am. J. Pat. 1997;150:1687-1699). Por consiguiente, los inhibidores de la Fms interrumpen las señales de la M-CSF, comprometiendo los monocitos en la progresión de las células espumosas de los macrófagos, la supervivencia y réplica de los macrófagos y la señalización de la citoquina que participa en la progresión de la lesión.

[0552] El papel de la M-CSF y la Fms en el enfisema parece estar involucrado en la regulación del metabolismo de la elastina a través del control de las metaloproteínas matrices. La M-CSF juega un papel en la modulación de la acumulación y función de los macrófagos alveolares (MA) in vivo (Shibata et al,

Blood 2001, 98: pp. 2845-2852). Los ratones osteopetróticos (Op/Op) no tienen M-CSF detectable y muestran reducciones específicas en tejidos variables en el número de macrófagos. Por consiguiente, se ha hipotetizado que los AM disminuirían en número y alterarían la función en los ratones Op/Op debido a la ausencia de la M-CSF. Shibata et al encontró que los macrófagos identificados en las secciones de los pulmones disminuyeron en número en los ratones Op/Op de 20 días de edad pero no en los ratones Op/Op de más de 4 meses comparado con los hallazgos de los controles de camadas de la misma edad. El número de MA reuperado por el lavado broncoalveolar (LBA) también se redujo en los ratones Op/Op jóvenes pero no adultos comparado con los controles. Significativamente, los MA de los ratones Op/Op liberan niveles más altos de metaloproteinasas matrices (MPM) que los MA de los controles. Consistente con el aumento en la liberación de MPM, los ratones Op/Op tienen deposición anormal de elastina y desarrollan espontáneamente enfisema en la ausencia de evidencia molecular o celular de inflamación pulmonar. Por consiguiente, la modulación de la actividad de la metaloelastasa en los macrófagos mediante la M-CSF puede controlar la degradación de las fibras de elastina en los pulmones o los vasos sanguíneos.

[0553] Las células cancerígenas metastásicas causan destrucción ósea con fractura asociada, dolor, deformación e hipercalcemia debido a la producción de los factores osteoclastiogénicos incluyendo la M-CSF mediante células tumorales (Clohisy et al, Clin. Ortop. 2000, 373: 104-14). La union de la M-CSF a la Fms estimula la formación de oestoclástos y la actividad osteolítica (Kodama et al, J. Exp. Med. 1991, 173: 269-72; Feng et al, Endocrinology 2002, 143: 4868-74). Por

consiguiente, la inhibición de la actividad oestoclástica a nivel de la Fms ofrece un objetivo apremiante para el mejoramiento de la metástasis ósea.

[0554] La Nefritis es la inflamación de los riñones. Puede ser causada por ejemplo por una infección bacteriana de los riñones o la exposición a una toxina. Sin embargo, la nefritis con más frecuencia se desarrolla a partir de una reacción inmunológica anormal, lo que puede ocurrir, por ejemplo, cuando un anticuerpo ataca al riñón mismo o a un antígeno unido a las células del riñón, o cuando un complejo antígeno-anticuerpo formado en el cuerpo se une a las células del riñón en Algunos tipos de nefritis incluyen la infiltración de tejidos por los glóbulos blancos de la sangre y depósitos de anticuerpos. En otros tipos de nefritis, la inflamación puede consistir en la inflamación del tejido o cicatrización sin glóbulos blancos o anticuerpos. Además, la nefritis puede ocurrir en cualquier parte de los riñones. Con respecto a los glomérulos, el daño progresivo a los glomérulos provoca la producción de orina disminuya y que los productos metabólicos de desecho se acumulen en la sangre. Cuando el daño a los glomérulos es grave, las células inflamatorias y las células glomerulares heridas se acumulan comprimiendo los capilares dentro del glomérulo e interfiriendo con la filtración. Puede desarrollarse cicatrización, alterando la función renal y la reducción de la producción de orina. En algunos casos, puede formarse microtrombos en vasos sanguíneos pequeños, disminuyendo la función renal. Con menos frecuencia, la nefritis implica los tejidos tubulointersticiales, dicha inflamación se llama nefritis tubulointersticial. Cuando la inflamación daña los túbulos y los tejidos tubulointersticiales, los riñones pueden llegar a ser incapaces de concentrar la orina, eliminar (excretar) los productos de desecho metabólico del cuerpo, o balancear la excreción de sodio y otros electrolitos como el potasio. Cuando se dañan los túbulos y los tejidos tubulointersticiales, se

desarrolla a menudo insuficiencia renal. En consecuencia, la inhibición de la Fms ofrece un objetivo para la intervención terapéutica en la nefritis debido a la modulación de la respuesta inflamatoria comprometiendo la etiología de la enfermedad.

[0555] **La nefritis lúpica**, es decir, el involucramiento renal en el lupus eritomatoso sistémico (LES), es una enfermedad común con poca prognosis. Al menos tres mecanismos inmunopatogénicos de la nefritis lúpica se soportan en los datos experimentales. Primero, los complejos inmunes circulantes que consisten principalmente de ADN y el anti-ADN se depositan en el riñón. La activación del complemento resultante y la quematosis de los neutrófilos producto un proceso inflamatorio local. Segundo, la formación in situ de los complejos de antígeno y anticuerpo producen similarmente la activación del complemento y la lesión mediada por leucocitos. Tercero, los anticuerpos contra objetivos celular específicos puede producir lesión renal. Se observa un mecanismo adicional en pacientes con LES con el síndrome de anticuerpo antifosfolípido. Puede resultar trombosis glomerular a partir de la hipercoagulabilidad que acompaña a los anticuerpos dirigidos con los complejos de fosfolípidos y proteínas cargados negativamente. (es decir, VDRL de falso positivos biológicos, anticuerpos de anticardiolipina, y anticoagulantes lúpicos). La nefritis lúpica mesangial lupus está acompañada por hallazgos de diagnostico normales o con un grado moderado de proteinuria pero generalmente ausencia de hipertensión o sedimento urinario anormal. La glomerulonefritis proliferativa focal y difusa está frecuentemente asociada con el peor diagnostico de supervivencia renal y puede estar acompañada por el síndrome nefrótico, hipertensión significativa y sedimento de orina anormal. La nefritis lúpica

membranosa frecuentemente se presenta con proteinuria, alta o moderada, pero usualmente con sedimento urinario normal en ausencia de la hipertensión. La nefropatía lúpica mesangial está asociada generalmente con un pronóstico excelente, mientras que la nefropatía lúpica proliferativa, especialmente la variante difusa, está frecuentemente caracterizada por hipertensión, abatimiento de los glóbulos rojos y deterioro significativo de la función renal. El síndrome nefrótico en ausencia de hipertensión, el sedimento urinario activo o la hipocomplementemia sugieren la variante membranosa de la nefropatía lúpica. La nefropatía membranosa generalmente está asociada con un buen pronóstico y la conservación relativa de la función renal. Sin embargo, en la presencia de la proteinuria de rango nefrótico persistente, la nefropatía lúpica membranosa puede conducir a la pérdida de la función renal y enfermedad renal en etapa final (ESRD). Por consiguiente, la inhibición de la Fms ofrece un objetivo para la intervención terapéutica del lupus debido a la modulación de la respuesta inflamatoria que involucra la etiología de la enfermedad

[0556] La acumulación de macrófagos es una característica prominente de muchas formas de glomerulonefritis. La proliferación local de macrófagos en el riñón ha sido descrita en humanos y la glomerulonefritis experimental puede tener un papel importante en el aumento de la respuesta inflamatoria. Isbel et al (Nefrol Dial Transplant 2001, 16: 1638-1647) examinaron la relación entre la proliferación local de macrófagos y la expresión renal de la M-CSF. La expression Glomerular y tubulointerstitial de la M-CSF se encontró estar regulada en la glomerulonefritis humana, siendo ésta más prominente en la formas proliferativas de la enfermedad. Debido a que esto se correlaciona con la proliferación local de macrófagos, se

sugiere que el aumento de la producción de M-CSF renal juega un papel importante en la regulación de la proliferación local de los macrófagos en la glomerulonefritis humana. En un modelo de inflamación renal (UUO- obstrucción uretérica unilateral) el tratameitno con anticuerpo anti-Fms redujo la acumulación de macrófagos (Le Meur et.al., J Leukocite Biology, 2002, 72: 530-537). Por consiguiente, la inhibición de la Fms ofrece un objetivo para la intervención terapéutica de la glomerulonefritis.

[0557] La Resistencia a la insulina y la obesidad son una característica distintiva de la diabetes tipo II y existe una fuerte correlación entre la resistencia a la insulina y la acumulación de grasa visceral abdominal (Bjorntrop, Diabetes Metab. Res. Rev., 1999, 15: 427-441). La evidencia actual sugiere que la acumulación de macrófagos en el tejido adipose libera TNF-a y otros factores que causan cambios de en los adipocitos (hipertrofia, lipólisis, sensibilidad reducida a la insulina) y también promueve la resistencia a la insulina en los tejidos circundantes. Por lo tanto, la acumulación de macrófagos en la diabetes tipo II es importante para la progresión de la enfermedad. En consecuencia, la inhibición de la Fms tiene potencial al prevenir el desarrollo de la resistencia a la insulina y la hiperglicemia.

[0558] De forma similar, la observación de que la producción de M-CSF, el principal factor de crecimiento de macrófagos, aumenta en los tejidos durante la inflamación señala el papel de la Fms en enfermedades como por ejemplo, las enfermedades inflamatorias. Más particularmente, debido a los niveles elevados de M-CSF encontrados en el estado de la enfermedad, la modulación de la actividad de la Fms puede mejorar la enfermedad asociada con el aumento en los niveles de M-CSF.

[0559] Los inhibidores de la Fms pueden ser útiles al tratar indicaciones inflamatorias y autoinmunes incluyendo, pero no limitadas a , artritis reumatoide, osteoartritis, artritis psoriatica, psoriasis, dermatitis, espondilitis anquilosante, polimiositis, dermatomiositis, esclerosis sistémica, artritis idiopática juvenil, polimialgia reumática, enfermedad de Sjogren, histiocitosis celular de Langerhan (LCH), enfermedad de Still, síndrome de intestino inflamatorio, colitis ulcerativa, enfermedad de Crohn, lupus eritematoso sistémico (LES), rechazo de trasplante, enfermedad pulmonar obstructiva crónica (EPOC), enfisema, enfermedad de Kawasaki, síndrome hemofagocítico (síndrome de macrófagos activados), reticulohistiocitosis multicéntrica, y aterosclerosis , trastornos metabólicos, incluyendo, pero limitados a, diabetes tipo I, diabetes tipo II , resistencia a la insulina, hiperglucemia, obesidad, y lipólisis, trastornos de la estructura ósea, mineralización y formación y resorción ósea, incluyendo pero no limitada a, osteoporosis, osteodistrofia, aumento del riesgo de fractura, enfermedad de Paget, hipercalcemia, osteolisis mediada por infección (osteomielitis, por ejemplo), y osteolisis periprotésica o desgaste mediado por residuos, enfermedades renales y genitourinarias, incluyendo pero no limitadas a, endometriosis, nefritis (por ejemplo, glomerulonefritis, nefritis intersticial, nefritis lúpica), necrosis renal tubular, complicaciones asociadas con la diabetes (por ejemplo, nefropatía diabética), e hipertrofia renal, trastornos del sistema nervioso, incluyendo, pero no limitados a, trastornos desmielinizantes (por ejemplo, esclerosis múltiple, síndrome de Charcot Marie Tooth), esclerosis lateral amiotrófica (ALS), miastenia gravis, polineuropatía desmielinizante crónica, otros trastornos desmielinizantes, ataques, enfermedad de Alzheimer y enfermedad de Parkinson, dolor, incluyendo pero no limitado a, dolor crónico, dolor agudo, dolor inflamatorio, dolor neuropático, dolor

en los huesos, enfermedades malignas, incluyendo, pero no limitadas a, mieloma múltiple, leucemia mieloide aguda (LMA), leucemia mieloide crónica (LMC), cáncer de pulmón, cáncer de páncreas, cáncer de próstata, cáncer de seno, cáncer de ovario, neuroblastoma, sarcoma, osteosarcoma, tumores de células gigantes (por ejemplo, tumor de células gigantes del hueso, tumor de células gigantes de la vaina del tendón (TTCG)), sinovitis villonodular pigmentada (SVP), angiogénesis tumoral , melanoma, glioblastoma multiforme, glioma, otros tumores del sistema nervioso central, metástasis cerebral , metástasis óseas osteolíticas, metástasis de tumores de otros tejidos, y otras enfermedades mieloproliferativas crónicas como la mielofibrosis, vasculitis, incluyendo pero no limitadas a la enfermedad vascular de colágeno, poliarteritis nodosa, enfermedad de Behcet, sarcoidosis, fibere familiar mediterránea, vasculitis Churg-Strauss, arteritis temporal, arteritis de células gigantes, arteritis de Takayasu; indicaciones oftalmológicas, incluyendo pero no limitadas a uveítis, escleritis, retinitis, degeneración macular, neovascularización coroidea, retinopatía diabética;, indicaciones de enfermedades infecciosas, enfermedades hereditarias, incluyendo pero no limitadas a querubismo, neurofibromatosis incluyendo pero no limitada a infecciones asociadas con el virus de inmunodeficiencia humana, virus de la hepatitis B, virus de la hepatitis C, anaplasmosis granulocítica humana; desórdenes de almacenamiento lisosomal, incluyendo pero no limitados a la enfermedad de Gaucher, enfermedad de Fabry, enfermedad de Niemann-Pick, indicaciones gastrointestinales, incluyendo pero no limitadas a cirrosis de hígado; indicaciones pulmonares, incluyendo pero no limitadas a fibrosis pulmonar, lesión pulmonar aguda (por ejemplo, inducidas por ventilador, humo o tóxinas), isquemia global, e indicaciones quirúrgicas,

incluyendo pero no limitadas a cirugía de bypass (cardiopulmonar) , cirugía vascular, e injertos vasculares.

[0560] **Kit:** **Objetivo Quinasa** Kit (es decir oncógeno viral del sarcoma felino 4 de Hardy-Zuckerman) es una tirosina quinasa de 109.9 kDa de tipo transmembrana codificada por el cromosoma 4q12 (símbolo: KIT). La proteína tirosina quinasa receptora (RPTKs) regula las cascadas de transducción de los signos clave que controlan el crecimiento y la proliferación celular. La quinasa receptora kit de Factor de Células Estaminales (SCF) es una RPTK de transmembrana tipo II que incluye cinco dominios de inmunoglobulina extracelulares (IG), un único dominio transmembrana y una división de dominio citoplásmico separa do por el segmento de inserto de la quinasa. La quinasa Kit juega un papel importante en el desarrollo de los melanocitos, las células fibrosas, las células germinales y las células hematopoyéticas.

[0561] El factor de Células Estaminales (SCF) es una proteína codificada por el locus S1, y también ha sido llamada ligando kit (LK) y factor de crecimiento de células estaminales (MGF), con base en las propiedades biológicas usadas para identificarla (revisada en Tsujimura, Patol Int 1996, 46:933-938; Lovely, et al., J. Endocrinol 1997, 153:337-344; Vliagoftis, et al., Clin Immunol 1997, 100:435-440; Broudy, Blood 1997, 90:1345-1364; Pignon, Hermatol Célula Ter 1997, 39:114-116; y Lyman, et al., Blood 1998, 91:1101-1134.). Aquí la abreviatura SCF se refiere al ligando de la quinasa Kit.

[0562] El SCF se sintetiza como una proteína de tipo transmembrana con un peso molecular de 220 o 248 Dalton, dependiendo del acoplamiento alternativo de la mARN para codificar el exón 6. La proteína más grande puede fraccionarse para

formar una proteína glicolisada soluble que se dimeriza de forma no covalente. Las formas de unión del soluble y la membrana del SCF pueden unirse para activar la quinasa Kit. Por ejemplo, en la piel, el SCF se expresa predominantemente mediante los fibroblastos, queratinocitos y las células endoteliales, las cuales modulan la actividad de los melanocitos y las células fibrosas que expresan la quinasa Kit. En los huesos, las células estromales de la médula expresan el SCF y regulan la hematopoyesis de las células estaminales que expresan la quinasa Kit. En el tracto gastrointestinal, las células epiteliales intestinales expresan el SCF y afectan las células intersticiales del Cajal y los linfocitos intraepiteliales. En la testis, las células de sertoli células y las células granulosas expresan el SCF el cual regula la espermatogénesis mediante la interacción con la quinasa Kit en las células germinales.

[0563] De acuerdo con OMIM, la señalización de la quinasa Kit es esencial para el crecimiento de las células germinales primordiales tanto in vivo como in vitro. Se han identificado muchos efectores corriente abajo de la vía de señalización de la quinasa KIT en otros tipos de células, pero se desconoce como estas moléculas controlan la supervivencia y proliferación de las células germinales primordiales. La determinación de los efectores de la quinasa KIT que actúa en las células germinales primordiales ha estado obstruida por la falta de métodos efectivos para manipular fácilmente la expresión germinal de estas células. De Miguel et al. (2002) trató este problema al probar la eficacia de la transferencia germinal mediada por retrovirus para la manipulación de la expresión germinal en células germinales mamíferas. Encontraron que las células germinales primordiales pueden infectarse exitosamente con distintos tipos de retrovirus. Usaron este método para demostrar

un papel importante de la AKT1 al regular el crecimiento de las células germinales primordiales (OMIM MIM Number: 164920: 04/17/2006).

[0564] La expresión aberrante y/o activación de la Kit ha estado implicada en distintas estados patológicos. Por ejemplo, la evidencia de la contribución de la Kit en la patología neoplásica incluye la asociación con leucemias y mastocitoma, cáncer de pulmón de células pequeñas, cáncer testicular y algunos cánceres del tracto gastrointestinal y el sistema nervioso central. Adicionalmente, la kit ha estado implicada al jugar un papel en la carcinogénesis de los sarcomas del tracto genital femenino de origen neuroectodermal, y la neoplasia de célula Schwann asociada con la neurofibromatosis. Se ha encontrado que las células fibrosas están involucradas en la modificación del microambiente tumoral y en aumentar el crecimiento tumoral (Yang et al., J Clin Invest. 2003, 112:1851-1861; Viskochil, J Clin Invest. 2003, 112:1791-1793).

[0565] Los inhibidores de la Kit pueden ser útiles al tratar afeccioes malignas, incluyendo, pero no limitadas a , mastocitomas, cáncer de pulmón de célula pequeña, cáncer de pulmón de célula no pequeña (NSCLC), cáncer testicular, cáncer pancreático , cáncer de seno, carcinoma de célula de merkel, carcinomas del tracto genital femenino, sarcomas de origen neuroectodermal, carcinoma colorectal, carcinoma in situ, tumores estromales gastrointestinales (GIST), angiogenesis tumoral, glioblastoma, astrocitoma, neuroblastoma, neoplásia de célula Schwann asociada con neurofibromatosis, neurofibromatosis no asociada con neoplásia de célula Schwann, leucemia mielocítica aguda, leucemia linfocítica aguda, leucemia mielogenosa aguda, mastocitosis, melanoma, y mastocitomas en perros; enfermedad cardiovascular, incluyendo, pero no limitada a aterosclerosis, cardiomiopatia, falla

cardiaca, hipertensión pulmonar; indicaciones inflamatorias y autoinmunes, incluyendo, pero no limitadas a , alergia, anafilaxis, asma, artritis reumatoide, rinitis alérgica, esclerosis múltiple, síndrome de intestino inflamatorio, rechazo de trasplante, , hipereosinofilia, urticaria y dermatitis; indicaciones gastrointestinales, incluyendo pero no limitadas a enfermedad de reflujo gastroesofageal (GERD), esofagitis, y úlceras del tracto gastrointestinal; indicaciones oftálmicas, incluyendo pero no limitadas a uveitis y retinitis; e indicaciones neurológicas, incluyendo pero no limitadas a migraña.

[0566] **Flt3:** Objetivo Quinasa Flt3 (es decir, tirosina quinasa 3 similar a la Fms) es una tirosina quinasa de tipo transmembrana de 112.8 kDa codificada por el cromosoma 13q12 (símbolo: FLT3). De acuerdo con OMIM, Rosnet et al. (Genomics 1991, 9: 380-385) aislaron el novedoso miembro de los receptores clase 3 discutidos anteriormente. Demostraron que este gen de la familia tirosina quinasa, llamado FLT3, tiene fuertes similitudes de secuencia con otros miembros del grupo. La células estaminales linfohematopoyéticas sirven como un estanque para virtualmente todas las células sanguíneas pero constituyen solo aproximadamente el 0.01% de las células medulares humanas o murinas. La capacidad de aislar y expandir esta población tiene aplicación clínicas en trasplantes de médula ósea para el cáncer y enfermedades genéticas. Small et al. (Proc. Nat. Acad. Sci. 1994, 91: 459-463) clonaron el cADN de la tirosina quinasa 1 de célula estaminal, el homólogo humano de la murina Flk2/Flt3, a partir de una biblioteca enriquecida con células CD34+ estaminales hematopoyéticas. El cADN codificó a una proteína de 993 amino ácidos con 85% de identidad y 92% de similitud al homólogo murino. La STK1, que es idéntica a la FLT3, es un miembro de la familia tirosina de receptor

tipo III que incluye las KIT, FMS, y el receptor de crecimiento derivado de las plaquetas. La expresión de la STK1 en la sangre y la médula humanas está restringida a las células CD34+ células, una población enriquecida con células estaminales/progenitoras. Los oligonucleótidos antisentido dirigidos contra las secuencias de la STK1 inhiben la formación de colonias hematopoyéticas, más fuertemente en los cultivos de médula ósea a largo plazo. Los datos sugieren que la STK1 puede funcionar como un receptor del factor de crecimiento en las células estaminales y/o progenitoras hematopoyéticas (OMIM MIM Número: 136351: 03/03/2005).

[0567] Levis et al., declararon que las mutaciones de duplicación interna en tándem (ITD) de la tirosina quinasa receptora FLT3 se ha encontrado en 20% a 30% de los pacientes con leucemia mieloide aguda (AML). Estas mutaciones activan constitutivamente el receptor y parecen estar asociadas con un pronóstico deficiente. En su estudio, se realizaron ensayos citotóxicos de respuesta a la dosis con AG1295, un inhibidor de la tirosina quinasa activo contra la FLT3, en blastos primarios de pacientes con AML, y encontraron que el AG1295 fue específicamente citotóxico para los blastos de la AML blasts que alojaban mutaciones de la FLT3/ITD. Ellos sugieren que estas mutaciones contribuyen al proceso leucémico y que el receptor de la FLT3 receptor representa un objetivo terapéutico en AML (Levis et al., Blood 2001, 98:885-887). El inhibidor de la Flt3 puede ser útil al tratar la leucemia mieloide aguda, el síndrome mielodisplásico y la leucemia linfoblástica aguda.

[0568] **TrkA:** Objetivo Quinasa TrkA (es decir, tirosina quinasa neurotrófica, receptor tipo 1) es una tirosina quinasa de 140 kDa codificada por el cromosoma

1q21-q22 (símbolo: NTRK1). Los inhibidores de la TrkA pueden ser útiles al tratar el dolor (como dolor crónico, dolor neuropático), cáncer (como cáncer de próstata , cáncer de pulmón, leucemia mieloide, cáncer pancreático), desórdenes alérgicos (como asma), artritis, retinopatía diabética, degeneración macular y psoriasis.

[0569] La TrkA es miembro receptor de plasma compuesto de un dominio extracelular (responsable por la unión de alta afinidad con el factor de crecimiento nervioso, (NGF), un segmento de la transmembrana y un dominio intracelular de la proteína tirosina quinasa (responsable por transmitir la señal del NGF para iniciar y coordinar las respuestas neuronales). La unión del NGF induce a la TrkA a agruparse en la membrana y activa la quinasa. La quinasa inicia una cascada de eventos de fosforilización la proteína a través de múltiples vías incluyendo SHC/Ras/MAPK, PI3K y PLCg1. No se espera que el inhibidor de la quinasa TrkA evite la unión entre el NGF/TrkA, pero podría evitar la transducción estaminal corriente abajo.

[0570] El Factor de Crecimiento Nervioso (NGF) es producido por varios tejidos y células inflamatorias durante la lesión del tejido y la respuesta inmune del anfitrión. Éste se inicia y mantiene la hipersensibilidad a los estímulos entrantes (hiperalgesia) y la percepción de estímulos no nocivos (alodinia). A través de su receptor TrkA de alta afinidad, el NGF aumenta el estado excitación de las neuronas sensoriales que van hacia el sistema nervioso central (sensibilidad periférica), y aumenta la liberación de transmisores de la médula espinal dorsal (sensibilidad central). En las pruebas críticas, una única inyección subcutánea del NGF generó hiperalgesia que persistió hasta por 7 semanas. En dosis de más de 0.1 microgramos/kg, el NGF causó dolor muscular que varió de leve a moderado, principalmente en la

musculatura bulbar y troncal. El NGF intravenoso produjo efectos sistémicos más tempranos y pronunciados (Petty et al, 1994, Ann Neurol. 36: 244-6). De forma inversa, los inhibidores de la quinasa TrkA podrían usarse para tratar enfermedades de estados mejorados de la nociception.

[0571] En la inflamación de la pata trasera, la ligación del nervio espinal y modelos de dolor neuropático inducidos por estreptozoticina, inducida por el Adyuvante Completo de Freund (CFA), una sola inyección intraperitoneal del anti-NGF estableció la alodinia táctila a partir del día 3 a 7 después del tratamiento, en el modelo de ratón CCI, el anti-NGF reversó la alodinia táctil cuando se administró 2 semanas después de la cirugía. La administración repetida de este anticuerpo a los ratones CCI por 3 semanas produjo una reversión sostenida de la alodinia táctil (Wild et al, 2007, J. Farmacol. Exp. Ter. 322:282-287).

[0572] Los tumores de próstata que se han metastizado en el hueso frecuentemente inducen dolor óseo que puede ser difícil de controlar completamente ya que parece ser conducido simultáneamente por los mecanismos inflamatorios, neuropáticos y tumorigénicos. El Anti-NGF produjo una reducción significativa en el comportamiento relacionado con el dolor óseo en etapas tempranas y tardías. Esta terapia no influenció la remodelación ósea inducida por el tumor, la proliferación de osteoblastos, la osteoclastogénesis, el crecimiento tumoral, o los marcadores de la innervación sensorial o simpatética en la piel o los huesos. Todas las fibras nerviosos que inervan el hueso expresan la TrkA y la p75, y estos son receptores a través de los cuales el NGF sensibiliza y/o activa los nociceptores (Halvorson et al, 2005, Cáncer Res. 65:9426-35).

[0573] En pacientes con asma leve debido a la exposición a alérgenos de gato, la expresión del NGF fue fuertemente inducida en las células epiteliales, los fibroblastos, vasos sanguíneos y en pocas células infiltrantes. El mARN de la TrkA y los niveles de proteína en las biopsias bronquiales aumentaron significativamente después de la exposición al alérgeno en las células cebadas infiltrantes antes del inicio de los síntomas (Kassel et al, 2001, Clin Exp Allergy 31:1432-40).

[0574] La reacción de fase tardía en el asma después de la provocación del alérgeno está dominada por el influjo de eosinófilos activados dentro de lumen bronquial, lo que se relaciona con la liberación de productos eosinofílicos en la vías aéreas que aumentan la severidad de la enfermedad. La viabilidad y activación de los eosinófilos de los pacientes con asma leve mejoraron significativamente después de la estimulación del NGF. La adición de anticuerpos neutralizantes anti NGF *ex vivo* anulan los efectos (Nassentein et al, 2003, J Exp Med 198:455-467). Los inhibidores de la quinasa TrkA podrían disminuir este loop paracrino ente el tracto respiratorio y las células cebadas infiltrantes así como los eosinófilos endobronquiales, y por lo tanto ser útil para el tratamiento del asma y otros desórdenes alérgicos.

[0575] **TrkB:** Objetivo Quinasa TrkB (es decir, tirosina quinasa neurotrófica, receptor, tipo 2) es una tirosina quinasa de 145 kDa codificada por el cromosoma 9q22.1 (Símbolo: NTRK2). Los inhibidores de la TrkB pueden ser útiles al tratar varios cánceres y sus metástasis (como cáncer de próstata , cáncer pulmón, tumores de Wilms, neuroblastomas, y cáncer pancreático), y varias neuropatias (como, apoplejía, esclerosis múltiple, mielitis transversa, y encefalitis).

[0576] En pruebas clínicas con BDNF recombinante, se desarrolló parestesia en el sitio de la inyección subcutánea (Coulie et al, 2000, Gastroenterology 119:41-50). La infusión intratecal de BDNF en humanos también indujo parestesia y fiebre como efectos adversos (Ochs et al, 2000, Amiotrof Lateral Scler Oter Motor Neuron Disord. 1:201-6). La parestesia crónica frecuentemente es un síntoma de una enfermedad neurológica subyacente o daño nervioso traumático. La parestesia puede ser causada por desórdenes que afectan al sistema nervioso central, como apoplejía y ataques sistémicos transitorios (mini-apoplejías), esclerosis múltiple, mielitis transversa, y encefalitis. Ya que el BDNF se une a la TrkB específicamente con alta afinidad estos efectos neuropáticos son mediados mediante la señalización de la TrkB. De este modo, los inhibidores de la quinasa Trkb pueden ser útiles al tratar ciertos pacientes con neuropatias.

[0577] Se sabe que el BDNF actúa en la sinapsis entre las neuronas sensoriales primarias y del asta dorsal espinal afectan la transmisión de dolor durante la inflamación. El aferente primario es la única fuente de BDNF en la médula espinal, y está sobre regulada en el ganglio de la raíz dorsal (DRG) por el NGF unos pocos días después de la inflamación y es transportado y liberado en el asta dorsal superficial de forma dependiente a la actividad. La expresión de la TrkB en el asta dorsal también aumenta pocos días después de la inflamación . Estos hallazgos sugieren que el BDNF puede actuar durante un periodo restringido en la fase temprana de la inflamación. A través de la TrkB, el BDNF activa los distintos canales: (1) los canales de los receptores de potencial transitorio (TRPC3), que producen una respuesta lenta al abrir el canal de un catión no receptivo; y (2) el canal Na+, que media una rápida despolarización en el hipocampo. Estos canales

están fuertemente asociados con el dolor inflamatorio. El Anti-BDNF aumentó significativamente el umbral de retirada en tratas tratadas con CFA, un modelo de dolor inflamatorio. Ya que el antisuero no afectó la hinchazón en el sitio de la inyección de CFA, el componente residual puede deberse a la sensibilidad periférica (Matayoshi et al, 2005, J Fisiol. 569:685-95).

[0578] En pacientes con neuroblastomas, se encontró que la co-expresión de TrkB y BDNF, la co-expresión de TrkB con amplificación de N-Mic a, y expresión de TrkB truncada han estado asociada con un resultado clínico deficiente (Nakagawara et al, 1994, Mol Célula Biol. 14:759-767). La co-expresión de la TrkB con su ligando BDNF puede generar un loop de retroalimentación positivo a través de loops autocrino y paracrino. También las truncaciones de la TrkB encontradas en estos tumores generan formas activadas de la proteína tirosina quinasa intracelular. Las señales de la TrkB constitutivamente activas a través de distintas vías promueven la iniciación, progresión y metástasis del cáncer. Estas quinasas TrkB truncadas también fueron encontradas en el carcinoma hepatocélular (Yang et al, 2005, Cáncer. Res 65:219-225). Así que, los inhibidores de la TrkB pueden tratar la subpoblación de pacientes con cáncer con vía de la TrkB activad.

[0579] En pacientes con cáncer pancreático, la expresión de la TrkB se correlaciona con la invasión perineural, el margen retroperitoneal positivo y una latencia menor de desarrollar metástasis de hígado (Sclabas et al, 2005, Clin. Cáncer. Res V11:440-449). Mecánicamente, la TrkB activa la vía de la PI3K para suprimir los anoikis (apoptosis que resulta de las interacciones célula-matriz) el cual es una de las barreras fisiológicas para la metástasis. La inhibición de la quinasa TrkB puede romper la resistencia a los anoikis de los tumores en metástasis (Douma

et al, 2004, Nature 430:1034-9). De modo que, los inhibidores de la TrkB pueden ser de utilidad en amplio rango de tipos de tumores.

[0580] **TrkC:** Objetivo Quinasa TrkC (es decir, tirosina quinasa neurotrófica, receptor, tipo 3) es una tirosina quinasa de 145 kDa codificada por el cromosoma 15q25 (symbol: NTRK3). Los inhibidores de la TrkC pueden ser útiles al tratar el dolor (como dolor crónico, dolor neuropático), cáncer (como cáncer de pulmón, cáncer de seno, cáncer pancreático , nefroma mesoblástico, fibrosarcoma infantil, neuroblastoma, cáncer gástrico), y desórdenes de pánico.

[0581] Con el involucramiento de la TrkC en los cambios moleculares y celulares se han indicado ataques de pánico subyacentes y dependencia al opiato (Gallego et al., Front Behav. Neurosci., 2010, 3:60). La expresión de la TrkC en las neuronas mecanosensoras sugiere el papel de la inhibición de la quinasa TrkC en el tratamiento del dolor (J Comp. Neurol., 2008, 511(4):543-56.

[0582] La TrkC también está involucrada en distintos tipos de cáncer, por ejemplo neuroblastoma (J. Clin. Invest., 2010, 120(3):850-8), nefroma mesoblástico, fibrosarcoma infantil, y cáncer de mama secretante donde está presente la fusión del gen ETV6-NTRK3 (Pediatr. Radiol. 2009, 39(10):1066-74; J. Clin. Patol. 2009, 62(7):604-12) y cánceres que involucran mutaciones en la TrkC, tal como cáncer de pulmón, cáncer gástrico, y cáncer pancreático (Marchetti et al., Hum. Mutat. 2008, 29(5):609-16; Kubo et al., Carcinogenesis, 2009, 30(11):1857-64); y Kubo et al., Pancreas, 2009, 38(7):e200-6).

Ensayos de Actividad de la Quinasa

[0583] Pueden utilizarse diversos ensayos sobre la actividad de la quinasa para el ensayo sobre los moduladores activos y/o determinación de la especificidad de un modulador para una quinasa particular o un grupo de quinasas. Adicionalmente al ensayo mencionado en los ejemplos siguientes, alguien con destreza común en el arte sabrá de otros ensayos que pueden utilizarse y que pueden modificar un ensayo para una aplicación particular. Por ejemplo, pueden usarse los numerosos documentos que describen las quinasas.

[0584] Pueden utilizarse ensayos alternativas adicionales para unir las determinaciones. Por ejemplo, esta clase de ensayo puede formatearse ya sea en un formato de transferencia de energía de resonancia fluorescente (FRET) , o usar un formato AlfaScreen (ensayo homogéneo de proximidad luminescente amplificada) al variar los reactivos del donante y el receptor que se enlazan a la estreptavidina o al anticuerpo fósforoespecífico.

Técnicas Sintéticas Orgánicas

[0585] Existen en el arte una amplia gama de técnicas sintéticas orgánicas para facilitar la construcción de moduladores potenciales. Muchos de estos métodos sintéticos orgánicos se describen detalladamente en las fuentes de referencia usadas por aquellos que tienen habilidad ordinaria en el arte. Un ejemplo de tales referencias es March, 1994, Advanced Organic Chemistry; Reactions, Mechanisms and Structure, New York, McGraw Hill. De hecho, las técnicas útiles para sintetizar un modulador potencial de la función de la quinasa se encuentran

fácilmente disponibles para aquellos corticoesteroides en el arte de la síntesis química orgánica.

Formas o Derivados de Compuestos Alternativos

[0586] Los compuestos aquí contemplados se describen con referencia tanto a compuestos de fórmulas genéricas como específicas. Adicionalmente, los compuestos de la invención pueden existir en distintas formas o derivados, todos dentro del alcance de la presente invención. Las formas o derivados alternativas, 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 de cristales, sólidos polimórficos o amorfos, incluyendo hidratos y solvatos de los mismos y otras formas.

(a) Profármacos y Metabolitos

[0587] En adición a las presentes fórmulas y compuestos aquí descritos, la invención también incluye profármacos (profármacos generalmente farmacéuticamente aceptables), derivados metabólicos activos (metabolitos activos), y sus sales farmacéuticamente aceptables

[0588] Los profármacos son compuestos o sales farmacéuticamente aceptables de estos, que Cuandosi metabolizan bajo condiciones fisiológicas o cuando son convertidos mediante solventes, 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 inactiva, o menos activa que el compuesto activo, pero pueden brindar una o más

manejos ventajosos, administración o propiedades metabólicas. Por ejemplo, algunos profármacos son ésteres del compuesto activa; durante la metabolisis, el grupo de ésteres es dividido para producir el medicamento activo. Los ésteres incluyen, por ejemplo, ésteres de un grupo ácido carboxílico, o derivados S-acil u O-acil de los grupos tiol, alcohol, o fenol. En este contexto, un ejemplo común es un éster alquilo de un ácido carboxílico. Los profármacos también pueden incluir variantes donde un grupo -NH del compuesto ha sufrido una acilación, tal como la posición 1 del 1H-pirrol[2,3-b]anillo de piridina, o el nitrógeno del grupo sulfonamida de compuestos aquí descritos, donde la división del grupo acilo brinda un grupo sin –NH del fármaco activo. Algunos profármacos son enzimáticamente activados para producir el compuesto a activo o un compuesto puede sufrir una reacción química adicional para producir el compuesto activo. Los profármacos pueden proceder de la forma del profármaco para activar la forma en un solo paso o pueden tener una o más formas intermedias que en sí tienen la actividad o pueden ser inactivas.

[0589] Como se describe en *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermut, Academic Press, San Diego, CA, 2001), los profármacos pueden dividirse conceptualmente en dos categorías no exclusivas, los profármacos bioprecursores y los profármacos portadores. Generalmente, los profármacos bioprecursores son compuestos que son inactivos o tienen una actividad menor comparada con el compuesto del fármaco activo correspondiente, que contiene un o más grupos protectores y se convierten en una forma activa mediante el metabolismo o por solvolisis. Tanto la forma del fármaco activa como los productos metabólicos

liberados deben tener baja toxicidad aceptable. Típicamente, la formación de un compuesto de fármaco activo involucra un proceso o reacción metabólica que es una de los siguientes tipos:

[0590] Reacciónes oxidativas: Las reacciónes oxidativas son ejemplificadas sin limitación por las reacciónes tales como la oxidación del alcohol, carbonilo, y las funcionalidades ácidas, la hidroxilación de los carbonos alifáticos, la hidroxilación de los átomos de carbono alicíclicos, la oxidación de átomos de carbono aromático, la oxidación de uniones dobles de carbono-carbono, la oxidación del nitrógeno que contiene grupos funcionales, la oxidación del silicio, fósforo, arsénico y sulfuro, la N- dealquilación oxidativa, O- dealquilación S- dealquilación oxidativa, la deaminación oxidativa, así como otras reacciónes oxidativas.

[0591] Reacciónes reductivas: Las reacciónes reductivas se ejemplifican sin limitación por las reacciónes como la reducción de las funcionalidades del carbonilo, la reducción de las funcionalidades del alcohol y de los enlaces dobles de carbono-carbono, la reducción de los grupos funcionales que contienen nitrógeno y otras reacciónes de reducción.

[0592] Reacciónes sin cambio en el estado oxidativo: Las reacciónes sin cambio en el estado de oxidación se ejemplifican sin limitación por las reacciónes tales como hidrolisi de ésteres y la división hidrolítica de los enlaces sencillos carbono-nitrógeno, la división hidrolítica de heterociclos no aromáticos, la hidratación y deshidratación en enlaces múltiples, los nuevos enlaces atómicos que resultan de reacciónes de deshidratación, la deshalogenación hidrolítica, la remoción de la molécula halida de nitrógeno, y otras reacciónes.

[0593] Los profármacos portadores son compuestos farmacéuticos que contienen una porción de transporte, por ejemplo, que mejora la absorción y/o entrega localizada a un sitio de acción. Preferiblemente para tal profármaco portador, el enlace entre la porción del fármaco y la porción de transporte es un enlace covalente, el profármaco es inactivo o menos inactivo que el compuesto del fármaco, el profármaco y la porción de transporte de liberación son aceptablemente no tóxicos. Para los profármacos donde la porción de transporte está prevista para mejorar la absorción, típicamente la liberación de la porción de transporte debe ser rápida. En otros casos, se desea utilizar un porción que brinde una liberación lenta, por ejemplo, ciertos polímeros u otras porciones, tales como ciclodextrinas. (Ver, por ejemplo, Cheng et al., U.S. Patent Publ. No. 20040077595, App. No. 10/656,838, aquí incorporado por referencia.) Dichos profármacos portadores son frecuentemente ventajosos para drogas administradas oralmente. En algunos casos, la porción de transporte brinda una administración focalizada de la droga. Por ejemplo el fármaco puede estar conjugado a un anticuerpo o fragmento de anticuerpo. Los profármacos portadores pueden, por ejemplo, ser usados para mejorar una o más de las siguientes propiedades: lipofilicidad aumentada, duración aumentada de los efectos farmacológicos, especificidad del sitio aumentad, toxicidad y reacciónes adversas disminuidas, y/o mejora de la formulación del fármaco (por ejemplo, estabilidad, solubilidad del agua, supresión de las propiedades organolépticas o físicoquímicas indeseables). Por ejemplo, la lipofilicidad puede ser aumentada por la esterificación de los grupos de hidroxilo con ácidos carboxílicos lipofílicos, o de grupos de ácido carboxílico con alcoholes, por ejemplo, alcoholes alifáticos. Wermut, *supra*.

[0594] Los metabolitos, por ejemplo, los metabolitos activos, se superponen con los profármacos descritos anteriormente, por ejemplo, los profármacos bioprecursores. De este modo, dichos metabolitos son compuestos farmacológicamente activas o compuestos que se metabolizan adicionalmente a compuestos farmacológicamente activos que son derivados que resultan de los procesos metabólicos del cuerpo de un sujeto. De estos, los metabolitos activos son aquellos compuestos farmacológicamente derivados. Para los profármacos, el compuesto del fármaco es generalmente inactivo de de una actividad menor al producto metabólico. Para los metabolitos activos, el compuesto principal puede ser un compuesto activa o un profármaco inactivo. Por ejemplo, en algunos compuestos, uno o más grupos alcoxi pueden ser metabolizados a grupos hidroxilo mientras que la actividad farmacológica de retención y/o los grupos carboxilo pueden ser esterificados, por ejemplo, la glucuronidación. En algunos casos, puede haber más de un metabolito, donde un metabolito intermedio se metaboliza adicionalmente para proporcionar un metabolito activo. Por ejemplo, en algunos casos un compuesto derivado que resulta de una glucoronidación metabólica puede ser inactivo o de una actividad menor, y puede ser metabolizado adicionalmente para proporcionar un metabolito activo.

[0595] Los metabolitos de un compuesto pueden ser identificados usando las técnicas de rutina conocidas en el arte, y sus actividades determinadas usando pruebas tales como las aquí descritas. Ver, por ejemplo, Bertolini et al., 1997, *J. Med. Chem.*, 40:2059-2064; Shan et al., 1997, *J Farm Sci* 86(7):756-757; Bagshawe, 1995, *Drug Dev. Res.*, 34:220-230; Wermut, *supra*.

(b) Tautómeros, Estereoisómeros, y Regioisómeros

[0596] Se entiende que algunos compuestos pueden exhibir tautomerismo. En tales casos, la fórmula suministrada aquí solo representa una de las posibles formas tautoméricas. Por lo tanto, para entender la fórmula aquí suministrada se pretende representar cualquier forma tautomérica de los compuestos representados y no están limitados meramente limitados a la forma tautomérica específica representada por los dibujos de la fórmula.

[0597] Así mismo, 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 covalentemente pero con diferencia 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 una o más formas estereoisoméricas (por ejemplo, enantiómeros o diastereómeros). De este modo, dichos compuestos pueden presentarse como estereoisómeros sencillos (es decir, esencialmente libres de otros estereoisómeros), racematos, y/o mezclas de enantiómeros y/o diastereómeros. Como otro ejemplo, los estereoisómeros incluyen isómeros geométricos, tales como *ces*- o *trans*-orientación de sustitutos de carbonos adyacentes de un doble enlace. Todos aquellos estereoisómeros sencillos, racematos y mezclas de los mismos están previstas para estar dentro del alcance de la presente invención. A menos que se especifique lo contrario, todas las formas esteroisoméricas se incluyen dentro de la fórmula aquí provista.

[0598] En algunas formas de realización, un compuesto quiral de la presente invención es un forma que contiene al menos 80% de un isómero sencillo (60% de

exceso enantiomérico (“e.e.”) o exceso diastereomérico (“e.d.”)), o al menos 85% (70% de e.e. o e.d.), 90% (80% e.e. o e.d.), 95% (90% e.e. o e.d.), 97.5% (95% e.e. o e.d.), o 99% (98% e.e. o e.d.). Como lo entienden generalmente aquellos versados en el arte, un compuesto ópticamente puro que tiene un centro quiral es uno que consiste esencialmente de uno de dos posibles enancióméros (es decir, es enanciociomericamente puro), y un compuesto ópticamente puro que tiene más de un centro quiral es aquel que es diastereoméricamente puro y enancioméricamente puro. En algunas formas de realización, el compuesto está presente en una forma ópticamente puro, dicha forma ópticamente pura se prepara y/o aísla mediante los métodos conocidos en el arte (por ejemplo, mediante técnicas de recristalización, técnicas sintéticas quirales (incluyendo síntesis de materiales de inicio ópticamente puros), y separación cromatográfica usando una columna quiral.

(c) Sales farmacéuticamente aceptables

[0599] A menos que se indique lo contrario, la especificación de un compuesto aquí descrito incluye sales farmacéuticamente aceptables de de dicho compuesto. De este modo, los compuestos aquí descritos pueden estar en la forma de sales farmacéuticamente aceptables, o pueden ser formuladas como sales farmacéuticamente aceptables Las formas de sales farmacéuticamente aceptables incluyen, sin limitación, mono, bes, tres, tetraquis, y así sucesivamente. Las sales farmacéuticamente aceptables son no tóxicas en las cantidades y concentraciones en las que son administradas. La Preparación de de dichas sales puede facilitar el uso farmacológico al alterar las características físicas de un compuesto sin evitar que ejerza su efecto fisiológico. Las alteraciones útiles de las propiedades físicas incluyen la disminución del punto de fusión para facilitar la administración

transmucosal y aumentar la solubilidad para facilitar la administración de concentraciones más altas del fármaco. Un compuesto de la invención puede representar un grupo lo suficientemente acídico, lo suficientemente básico o ambos grupos funcionales, y por consiguiente pueden reaccionar con cualquier número de bases inorgánicas u orgánicas, y ácidos inorgánicos u orgánicos, para formar una sal farmacéuticamente aceptable.

[0600] Las sales farmacéuticamente aceptables incluye sales de adición ácida tales como aquellas que contienen cloro, cloro, bromuro, yodo, hidrocloruro, acetato, fenilacetato, acrilato, ascorbato, aspartato, benzoato, 2-fenoxibenzoato, 2-acetoxibenzoato, dinitrobenzoato, hidroxibenzoato, metoxibenzoato, metilbenzoato, bicarbonato, butina-1,4 dioato, hexina-1,6-dioato, caproato, caprilato, clorobenzoato, cinamato, citrato, decanoato, formato, fumarato, glicolato, gluconato, glucarato, glucuronato, glucosa-6-fosfato, glutamato, heptanoato, hexanoato, esetionato, isobutirato, gama-hidroxibutirato, fenilbutirato, lactato, malato, maleato, hidroximaleato, metilmaleato, malonato, mielato, nicotinato, nitrato, isonicotinato, octanoato, oleato, oxalato, pamoato, fosfato, monohidrógenofosfato, dihidrógenofosfato, ortofosfato, metafosfato, pirofosfato, 2-fosfoglicerato, 3-fosfoglicerato, ftalato, propionato, fenilpropionato, propiolato, piruvato, quinato, salicilato, 4-aminosalicilato, sebacato, estearato, suberato, succinato, sulfato, pirosulfato, besulfato, sulfito, besulfito, sulfamato, sulfonato, bencenosulfonaA (es decir, besilato), etanosulfonaA (es decir, esilato), etano-1,2-desulfonato, 2-hidroxietanosulfonaA (es decir, esetionato), metanosulfonaA (es decir, mesilato), naftaleno-1-sulfonato, naftaleno-2-sulfonaA (es decir, napsilato), propanosulfonato, *p*-toluenosulfonaA (es decir, tosilato), xilenosulfonatos, ciclohexilsulfamato,

tartrato, y trifluoroacetato. Estas sales de adición ácida farmacéuticamente aceptables pueden prepararse usando el ácido correspondiente apropiado.

[0601] Cuando los grupos funcionales acídicos, tales como el ácido carboxílico o fenol están presentes, las sales farmacéuticamente aceptables también incluyen sales de adición básica tales como aquellas que contienen benzatina, cloroprocaina, colina, etanolamina, dietanolamina, trietanolamina, t-butilamina, diciclohexilamina, etilenediamina, N,N'-dibenciletilenediamina, 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-hestidina, L-glicina, L-lesina, y L-arginina. Por ejemplo, ver *Remington's Farmaceutical Sciences*, 19^{t} ed., Mack Publeshing Co., Easton, PA, Vol. 2, p. 1457, 1995. Estas sales de adición de base farmacéuticamente aceptables pueden prepararse usando la base correspondiente apropiada.

[0602] Las sales farmacéuticamente aceptables pueden prepararse mediante las técnicas estándar. Por ejemplo, la forma base libre de un compuesto puede disolverse en un solvente apropiado, tal como una solución acuosa o alcohol acuoso que contenga un ácido apropiado y luego aislarse al evaporar la solución. En otro ejemplo, una sal puede prepararse al reacciónar la base libre y el ácido en un solvente orgánico. Si el compuesto particular es un ácido, las sales farmacéuticamente aceptables deseadas pueden prepararse mediante cualquier método apropiado, por ejemplo, con el tratamiento de un ácido libre con una base inorgánica u orgánica apropiada.

(d) Otras formas de compuestos

[0603] En el caso de los agentes que son sólidos, aquellos que tienen habilidad ordinaria en el arte entienden que los compuestos y sales pueden existir en distintas cristales o formas polimórficas, o pueden ser formuladas como co-cristales o pueden ser en forma amorfa, o pueden ser una combinación de estas (por ejemplo, parcialmente cristalino, parcialmente amorfo, o mezclas de poliformas) todas las cuales están previstas para estar dentro del alcance de la presente invención y la fórmula especificada. Cuando las sales se forman por una adición ácido/base, es decir, una base libre o un ácido libre, el compuesto de interés forma una reacción ácido/base con una base de adición correspondiente o adición ácida, respectivamente, resultando o en una interacción de carga iónica, los co-cristales son una nueva especie química que se forma entre los compuestos neutrales, que resultan en el compuesto y una especie molecular adicional en la misma estructura del cristal.

[0604] En algunos casos, los compuestos de la invención se unen con un ácido o base, incluyendo sales de adición base tales como amonio, dietilamina, etanolamina, etilenediamina, dietanolamina, t-butilamina, piperazina, meglumina; sales de adición ácida, como acetato, acetilsalicilato, besilato, camsilato, citrato, formato, fumarato, glutarato, hidroclorato, maleato, mesilato, nitrato, oxalato, fosfato, succinato, sulfato, tartrato, tiocianato y tosilato; y aminoácidos tales como alanina, arginina, asparagina, ácido aspártico, cesteína, glutamina, ácido glutámico, glicina, hestidina, isoleucina, leucina, lesina, metionina, fenilalanina, prolina, serina, treonina, triptofan, tirosina o valina. En combinación. Al combinar el compuesto de la invención con un ácido o base, se forma preferiblemente un complejo amorfo más

bien que un material cristalino tal como una sal típica o co-cristal. En algunos casos, la forma amorfa del complejo se facilita mediante un procesamiento adicional, tal como secado por pulverización, métodos mecanoqúimicos tales como compactación por rodillo, o irradiación por microonda del compuesto principal mezclado con el ácido o base. Tales métodos también incluyen la adición de sistemas poliméricos iónicos y/o no iónicos, incluyendo, pero no limitados a, hidroxipropil metilcelulosa acetato succinaA (HPMCAS) y copolímero de ácido metacrílico (por ejemplo, Eudragit® L100-55), que estabiliza adicionalmente la naturaleza amorfa del complejo. Dicho complejo amorfo brinda varias ventajas. Por ejemplo, disminuyendo la temperatura de fusión relativa a la base libre facilita el procesamiento adicional, como la extrusión por fusión caliente, para mejorar adicionalmente las propiedades biofarmacéuticas del compuesto. También, el complejo amorfo es fácilmente desintegrable, lo que provee compresión mejorada para cargar el sólido en forma de cápsula o tableta.

[0605] Adicionalmente, la fórmula está prevista para cubrir formas hidratadas o solvatadas así como no hidratadas o no solvatadas de las estructuras identificadas. Por ejemplo, los compuestos indicados incluyen tanto formas hidratadas como no hidratadas. Otros ejemplos de solvatos incluyen las estructuras en combinación con un solvente apropiado, tal como isopropanol, etanol, metanol, dimetil sulfóxido, acetato etílico, ácido acético o etanolamina.

Formulaciones y Administración

[0606] Los métodos y compuestos se usarán típicamente en la terapia para sujetos humanos. Sin embargo, también pueden usarse para tratar indicaciones similares o idénticas en otros sujetos animales. Los compuestos aquí descritos

pueden ser administrados por distintas vías, incluyendo inyección (es decir, parenteral,

incluyendo intravenosa, intraperitoneal, subcutánea, e intramuscular), oral, transdérmica, , transmucosal, rectal, o inhalación. Dichas formas de dosificación permiten alcanzar las células objetivo. Otros factores son bien conocidos en el arte, e incluyen consideraciones tales como toxicidad y formas dosificación que retardan que el compuesto o composición ejerza sus efectos. Las técnicas y formulaciones generalmente pueden encontrarse en Remington: *The Science and Practice of Farmacy*, 21st edition, Lippincott, Williams y Wilkins, Filadelfia, PA, 2005 (aquí incorporado por referencia).

[0607] En algunas formas de realización, las composición incluirán portadores o excipients farmacéuticamente aceptables , tales como rellenos, aglutinantes, desintegrantes, deslizantes, lubricantes, agentes de complexión, solubilizadores, y surfactantes, que pueden escogerse para facilitar la administración del compuesto mediante una vía particular. Los ejemplos de portadores incluyen carbonato de calcio, fosfato de calcio, varias azúcares como la lactosa, glucosa, o sucrosa, tipos de almidón, derivados de celulosa, gelatina, lípidos, liposomas, nanopartículas, y similares. Los portadores también incluyen líquidos fisiológicamente compatible como solventes o 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 incluyen, por ejemplo, dióxido de silicio coloidal, gel de silicio, talco, silicato de magnesio, silicato de calcio, aluminosilicato de sodio, tresilicato de magnesio, celulosa en

polvo, celulosa macrocristalina, celulosa carboximetil, carboximetilcelulosa sódica entrecruzada, benzoato de sodio, carbonato de calcio, carbonato de magnesio, ácido esteárico, estearato de aluminio, estearato de calcio, estearato de magnesio, estearato de zinc, estearilo fumarato de sodio, siloide, stearowet C, óxido de magnesio, almidón, glicolato almidón de sodio, monostearato gliceril, dibehenato gliceril, palmitostearato gliceril, aceite vegetal hidrogenado, aceite de semilla de algodón hidrogenado, aceite de semilla de ricino, aceite mineral, polietilenglicol (por ejemplo, PEG 4048-8048), polioxietilenglicol, poloxámeros, povidona, crospovidona, croscarmelosa sódica, ácido algínico, caseína, ácido metacrílico, copolímero de divinilbenceno, docusato de sodio, ciclodextrinas (por ejemplo, 2-hidroxipropil-.delta.-ciclodextrina), polisorbatos (por ejemplo, polisorbato 80), cetrimida, TPGS (d-alfa-tocoferil polietilenglicol 1048 succinato), magnesio lauril sulfato, sodio lauril sulfato, ésteres de ácido graso de polietilenglicol o un éster de ácido graso de sorbitan polioxialquileno (por ejemplo, éster de polioxietileno sorbitan Tween®), ésteres de ácido graso de polioxietileo sorbitan, éster de ácido graso sorbitan, por ejemplo, a éster de ácido graso sorbitan de un ácido graso como ácido oleico, esteárico o palmítico, manitol, xilitol, sorbitol, maltosa, lactosa, lactosa monohidrato o lactosa secada por pulverización, sucrosa, fructosa, fosfato de calcio, fosfato de calcio dibásico, fosfato de calcio tribásico, sulfato de calcio, dextratos, dextran, dextrina, dextrosa, acetato de celulosa, maltodextrina, simeticona, polidextrosam, quitosan, gelatina, HPMC (hidroxipropilmetilcelulosas), HPC (hidroxipropilcelulosa), hidroxietilcelulosa, y similares.

[0608] En algunas formas de realización, puede usarse la administración oral. Las preparaciones farmacéuticas de uso oral pueden ser formuladas en formas de

dosificación oral convencionales como cápsulas, tabletas, y preparaciones líquidas como siropes, elíxires y gotas concentradas. Los compuestos aquí descritos pueden ser combinados con excipientes sólidos, proporcionando opcionalmente un mezcla resultante, y procesando o la mezcla de gránulos, después de añadir los auxiliares apropiados, si se desea, para obtener, por ejemplo, tabletas, tabletas recubiertas, cápsulas duras, cápsulas blandas, soluciones (por ejemplo, soluciones alcohólicas, acuosas o aceitosas) y similares. Los excipientes particulares son, rellenos como azúcar, incluyendo lactosa, glucosa, sucrosa, manitol, o sorbitol; preparaciones de celulosa, por ejemplo, almidón de maíz, almidón de trigo, almidón de arroz, almidón de papa, gelatina, goma tragacanto, metilcelulosa, hidroxipropilmetilcelulosa, carboximetilcelulosa de sodio (CMC), y/o polivinilpirrolidona (PVP: povidona); excipientes aceitosos, incluyendo aceites vegetales o aceitosos, como aceite de girasol, aceite de oliva, o aceite de hígado de bacalao. Las formulaciones orales también contienen agentes disgregantes, tales como polivinilpirrolidona entrelazada, agar, o ácido algínico, o una sal de la misma como alginato de sodio ; un lubricante, tal como estearato de magnesio; un plastificante como glicerol o sorbitol; a endulzante como sucrosa, fructosa, lactosa, o aspartame; un agente saborizante natural o artificial, como menda, aceite de gaulteria, sabor a cereza; o tintes o pigmentos, que pueden usarse para la identificación o caracterización de distintas dosis o combinaciones. También se proporcionan los núcleos de las grageas con los recubrimientos apropiados. Para es fin, pueden usarse soluciones de azúcar concentrada, los cuales pueden contener opcionalmente goma arábiga, talco, polivinilpirrolidona, gel de carbopol, polietilenglicol, y/o dióxido de titanio. Solución de laca y solventes orgánicos apropiados o mezclas de solventes.

[0609] Las formulaciones farmacéuticas pueden presentarse en formas de dosis unitaria que contienen una cantidad predeterminada de ingrediente activo por dosis unitaria. Dicha unidad puede contener, por ejemplo, 0.5 mg a 1 g, preferiblemente 1 mg a 700 mg, más preferiblemente 5 mg a 100 mg del compuesto de la invención (como base libre, solvato (incluyendo hidrato) o sal, en cualquier forma), dependiendo de la condición que se está tratando, la vía de administración y la edad, peso y condición del paciente. Las formulaciones de dosis unitarias preferidas son aquellas que contienen una dosis diaria, semanal, mensual, una sub-dosis o una fracción apropiada de la misma. Además, dichas formulaciones farmacéuticas pueden prepararse por cualquier de los métodos bien conocidos en el arte farmacéutico.

[0610] Las preparaciones farmacéuticas que pueden usarse oralmente incluyen cápsulas duras hechas de gelatina ("gelcaps"), así como cápsulas blandas selladas hecha de gelatina, y un plastificante como glicerol o sorbitol. Las cápsulas duras pueden contener los ingredientes activas en una mezcla con relleno tal como lactosa, aglutinantes como almidones, y/o lubricantes como talcos o estearato de magnesio y, opcionalmente estabilizadores. En las cápsulas blandas los compuestos activos pueden ser disueltos o suspendidos en líquidos apropiados, tales como ácidos grasos, parafina líquida o polietilenglicoles líquidos.

[0611] En algunas formas de realización, puede usarse una inyección (administración parenteral), como *por ejemplo,* intramuscular, intravenosa, intraperitoneal, y/o subcutánea. Los compuestos aquí descritos para la inyección pueden ser formulados en soluciones líquidas estériles, preferiblemente en buffers o soluciones fisiológicamente compatibles, como solución salina, solución de Hank, o

solución de Ringer. Las dispersiones también pueden prepararse en soluciones no acuosas, como glicerol, propilenglicol, etanol, polietilenglicoles líquidos, triacetina, y aceites vegetales. Las soluciones también pueden contener preservativos, como metilparabeno, propilparabeno, clorobutanol, fenol, ácido sórbico, timerosal, y similares. Adicionalmente, los compuestos pueden ser formulados en forma sólida, incluyendo, por ejemplo, formas liofilizadas, y ser redisueltos o suspendidos antes de usar.

[0612] En algunas formas de realización, puede usarse la administración transmucosal, tópica o transdérmica. En dichas formulaciones de los compuestos aquí descritos, se usan penetrantes apropiados para la barrera. Dichos penetrantes son generalmente conocidos en el arte, e incluyen por ejemplo, para la administración transmucosal , sales biliares y derivados de ácido fusídico. También pueden usarse detergentes para facilitar la permeación. La administración transmucosal, por ejemplo, puede realizarse mediante espray nasales o supositorios (rectal o vaginal). Las composiciones de los compuestos aquí descritos para la administración tópica pueden ser formulados como aceites, cremas, lociones, ungüentos y al escoger los portadores apropiados conocidos en el arte. Los portadores apropiados incluyen aceites vegetales o minerales, petróleo blanco (parafina blanca blanda), grasas o aceites de cadena ramificada, grasas animales y alcohol de alto peso molecular (mayor a C_{12}). En algunas formas de realización, los portadores se seleccionan de tal forma que el ingrediente activo sea soluble. Los emulsificadores, estabilizadores, humectantes y antioxidantes también se incluyen así como agentes de color o fragancia, si desea. Las cremas de aplicación tópica se formulan preferiblemente de una mezcla de aceite mineral, cera de abejas

autoemulsificante y agua en la cual la mezcla es el ingrediente activo, disueltas en una cantidad pequeña de solvente (por ejemplo, un aceite), sin mezclar. Adicionalmente, la administración por vía transdérmica puede incluir un parche o gasa transdérmica como un vendaje impregnado con un ingrediente activo y opcionalmente uno o más portadores o diluyentes conocidos en el arte. Para ser administrada en la forma de un sistema de administración transdérmica, la administración de la dosis será continua más bien que intermitente a lo largo del régimen de dosis.

[0613] En algunas formas de realización, los compuestos se administran como inhalantes. Los compuestos aquí descritos pueden ser formulados como polvos secos o suspensión de solución apropiada o aerosol. Los polvos y soluciones serán formuladas con aditivos apropiados conocidos en el arte. Por ejemplo, los polvos pueden incluir una base en polvo apropiada como lactosa o almidón, y las soluciones pueden incluir propilenglicol, agua estéril, etanol, cloruro de sodio y otros aditivos como ácido, álcali y sales amortiguadoras. Tales soluciones o suspensiones pueden ser administradas al inhalar un espray, bomba, atomizador, nebulizador y similares. Los compuestos aquí descritos también pueden usarse en combinación con otras terapias, Por ejemplo corticoesteroides tales como proprionato de fluticasona, dipropionato de beclometasona, acetonida triamcinolona, budesonida, y furoato de mometasona; beta agonestas como albuterol, salmeterol, y formoterol; agentes anticolinárgicos como bromuro de ipratroprium o tiotropium; vasodilatadores como treprostinal e iloprost; enzimas como ADNasa; proteínas terapéuticas, anticuerpos de inmunoglobulina; un oligonucléotido como ADN o ARN de una o dos cadenas, siRNA; antibióticos como tobramicina; antagonestas receptores muscarínicos;

antagonestas de leucotrieno; antagonestas de citoquina; inhibidores de proteasa; cromolin sódico; nedocril sódico ; y cromoglicato de sodio.

[0614] Las cantidades de los varios compuestos que serán administrados pueden determinarse mediante procedimientos estándar teniendo en cuenta factores como la actividad del compuesto (actividad *in vitro*, por ejemplo, el compuesto CI_{50} vs. objetivo, o actividad *in vivo* en modelos animales eficientes), resultados farmacocinéticos en modelos animales (por ejemplo, vida media biológica o biodisponibilidad), la edad, tamaño y peso del sujeto, y la afección asociada con el sujeto. La importancia de estos y otros factores es conocida para aquellos que tienen habilidad ordinaria en el arte. Generalmente una dosis estará en el rango de aproximadamente 0.01 a 50 mg/kg, también aproximadamente 0.1 a 20 mg/kg del sujeto bajo tratamiento. Pueden usarse dosis múltiples.

[0615] Los compuestos de la Fórmula I también pueden usarse en combinación con otras terapias para tratar la misma enfermedad. Tal combinación incluye la administración de compuestos y una o más terapias en distintos momentos, o la co-administración del compuesto y una o más terapias. En algunas formas de realización, la dosis puede modificarse por uno o más de los compuestos de la invención u otra terapias usadas en combinación, por ejemplo, reducción en la cantidad dosificada relativa al compuesto o terapia usados solos, mediante métodos bien conocidos para aquellos con habilidad ordinaria en el arte.

[0616] Se entiende que e uso en combinación incluye el uso con otras terapias, fármacos, procedimientos médicos etc., donde la otra terapia o procedimiento puede

administrarse en distintos periodos (por ejemplo, dentro de un periodo corto, como entre horas (por ejemplo, 1, 2, 3, 4-24 horas), o entre periodos más largos (por ejemplo, 1-2 días, 2-4 días, 4-7 días, 1-4 semanas)) que un compuesto aquí descrito, o al mismo tiempo que un compuesto aquí descrito. El uso en combinación también incluye el uso con terapia o procedimientos médicos que sean no suministradas o infrecuentes como una cirugía, junto con uno de los compuestos aquí descritos administrados dentro de un periodo corto o largo antes o después de la otra terapia o procedimiento. En algunas formas de realización, la presente invención proporciona la administración de un compuesto aquí descrito y una o más terapias con fármacos dadas por una vía de administración diferente o por la misma vía de administración. El uso en combinación de cualquier vía de administración incluye la administración de un compuesto aquí descrito y una o más terapias con fármacos administrados por la misma vía junto con cualquier formulación, incluyendo formulaciones donde los dos compuestos se enlazan químicamente en tal forma que mantengan su actividad terapéutica Cuandosi administran. En un aspecto, la otra terapia con fármacos puede ser co-administrada con uno de los compuestos aquí descritos. El uso en combinación por co-administración incluye la administración de co-formulaciones o formulaciones de compuestos enlazados químicamente, o la administración de dos o más compuestos en formulaciones separadas dentro de un periodo corto la una de la otra (por ejemplo, dentro de una hora, 2 horas, 3 horas, hasta 24 horas), administradas por la misma o distintas vías. La co-administración de las formulaciones separadas incluye la co-administración mediante un dispositivo. Por ejemplo el mismo dispositivo de inhalación, la misma jeringa, etc., o la administración por dispositivos separados dentro del mismo corto periodo el uno del otro. Las co-formulaciones de uno de los compuestos aquí descritos y una o más

terapias con fármacos administradas por la misma vía incluyen la Preparación de de los materiales juntos de tal forma que pudieran administrarse por un dispositivo, incluyendo los compuestos separados combinados en una formulación, o compuestos que son modificados de tal forma que se enlacen químicamente, manteniendo su actividad biológica. Dichos compuestos químicamente enlazados pueden tener un enlace que se mantenga sustancialmente *in vivo*, o el enlace puede romperse *in vivo*, separando los dos compuesto activos.

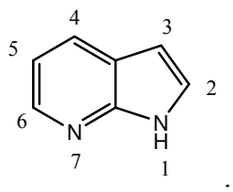
EJEMPLOS

[0617] Los ejemplos relacionados con la presente invención se describen más adelante. En la mayoría de los casos, pueden usarse técnicas alternativas. Los ejemplos están previstos para ser ilustrativos y no se limitan o restringen al alcance de la invención. Por ejemplo, cuando los compuestos adicionales se preparan siguiendo un protocolo de un Esquema para un compuesto particular, se entiende que las condiciones pueden varias. Por ejemplo, cualquiera de los solventes, tiempos de reacción, reactivos, temperaturas, condiciones de funcionamiento, u otros parámetros de reacción pueden variar usando solventes, reactivos, tiempos de reacción, temperaturas, condiciones de funcionamiento alternativas y similares, que estén fácilmente disponibles para aquellos con habilidad en el arte. En algunos ejemplos, el resultado de la espectrometría de masa indicado para un compuesto puede tener más de un valor debido a la distribución del isotopo de un átomo en la molécula, tal como un compuesto que tiene un sustituto de bromo o cloro.

[0618] A menos que se indique específicamente lo contrario, la enumeración de la Fórmula y la enumeración del grupo R usados en los siguientes ejemplos no se relaciona dicha enumeración en otras secciones de esta aplicación. Los activos y

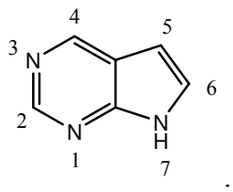
solventes usados en estos ejemplos pueden sustituirse fácilmente con alternativas apropiadas conocidas en el arte y un aislamiento de los productos se logra fácilmente mediante los métodos conocidos en el arte, incluyendo, pero no limitados, a extracción, cristalinización, y métodos cromatográficos.

[0619] La numeración del anillo de 1H-pirrolo[2,3-b]piridina en los siguientes ejemplos es la siguiente:



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[0620] La numeración del anillo de 7H-pirrolo[2,3-d]pirimidina en los siguientes ejemplos es la siguiente:

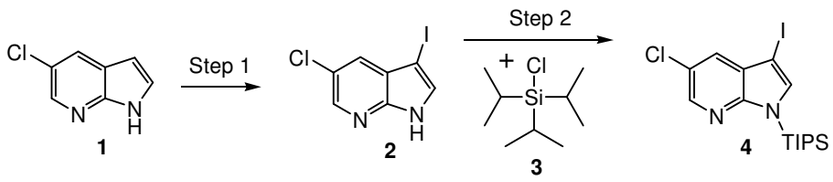


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Ejemplo 1: Síntesis del 5-cloro-3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina 4.

[0621] 5-Cloro-3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **4** se prepara en dos pasos a partir de 5-cloro-1H-pirrolo[2,3-b]piridina **1** como se muestra en el Esquema 1.

Esquema 1



*Paso 1 – Preparación de de 5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina (**2**):*

[0622] A una solución de 5-cloro-1H-pirrolo[2,3-b]piridina (**1**, 15.00 g, 98.31 mmol) en 300 mL de diclorometano bajo atmosfera o nitrógeno, se añade lentamente piridina (7.951 mL, 98.31 mmol) y monocloruro de yodo (110 mL, 1.0 M en diclorometano, 110 mmol) por 20 minutos. La reacción se agita a temperatura ambiente por 2 horas, luego se extingue con 100 mL del 1 M de tiosulfato de sodio pentahidratado acuoso. Se separan las capas, se recolectan los sólidos de la capa acuosa por filtración y se combinan con la capa orgánica. La capa orgánica se extrae con acetato de etilo, y las capas orgánicas se combinan y se lavan con salmuera, luego se concentran bajo vacío. El sólido resultante se lava con 20% acetato de etilo en hexano para proporcionar el compuesto deseado.

*Paso 2 – Preparación de 5-cloro-3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**4**):*

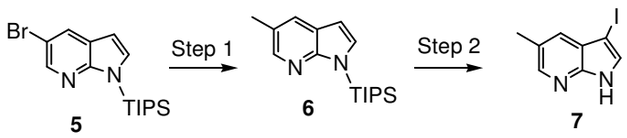
[0623] A 5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina (**2**, 16.50 g, 59.25 mmol) en 250.0 mL de N,N-dimetilformamida, se añade hidruro de sodio (3.10 g, 77.5 mmol). La reacción se agita a temperatura ambiente por 90 minutos, luego se añade lentamente cloruro de triisopropilsilil (**3**, 13.00 mL, 61.36 mmol). La reacción se agita a temperatura ambiente toda la noche, luego se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 20-100% acetato de etilo en hexano. Las

fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado (**4**, 10.0 g).

Ejemplo 2: Síntesis de 3-yodo-5-metil-1H-pirrolo[2,3-b]piridina 7.

[0624] 3-Yodo-5-metil-1H-pirrolo[2,3-b]piridina **7** se prepara en dos Pasos a partir de 5-bromo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **5** como se muestra en el Esquema 2.

Esquema 2



*Paso 1 – Preparación de5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**6**):*

[0625] En un matraz de fondo redondo, se combina el complejo [1,1'-bis(difenilfosfino)ferroceno] dicloropaladio(II) 1:1 con diclorometano (0.04 g, 0.05 mmol) con 10 mL de tolueno bajo una atmósfera de nitrógeno, y 5-bromo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**5**, 0.3 g, 0.8 mmol) y se añade 1 mL de tolueno gota por gota. La reacción se agita a 60 ^{o}C por 1 hora, luego a 90 ^{o}C por 30 minutos. La reacción se enfría a temperatura ambiente, se añade una solución de hielo/agua de ácido cítrico 0.1 N y pH 4, y la mezcla se extrae con acetato de etilo. La capa orgánica se lava con salmuera, se decolora con carbón vegetal, se filtra a través de celita y el filtrado se seca en sulfato de sodio. El sulfato de sodio se remueve por filtración y el filtrado se concentra bajo vacío para proporcionar el compuesto deseado(**6**, 218 mg).

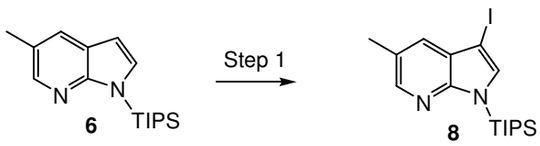
Paso 2 – Preparación de3-yodo-5-metil-1H-pirrolo[2,3-b]piridina (7):

[0626] A una solución de 5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**6**, 1 g, 2.0 mmol) en 10 mL de tetrahidrofurano, se añade yoduro (0.43 g, 1.7 mmol) en 5 mL de tetrahidrofurano. La reacción se agita a temperatura ambiente toda la noche, luego se extingue con 20 mL de tiosulfato de sodio acuoso1M y se extrae con acetato de etilo. Las capas orgánicas se combinan y se lavan con agua y salmuera, se secan en sulfato de sodio, se filtran y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con acetato de etilo y hexanos. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado como un sólido blanco (**7**, 20 mg). MS (ESI) $[M+H^+]^+ = 258.70$.

Ejemplo 3: Síntesis de 3-yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina 8.

[0627] 3-Yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **8** se prepara en un Paso a partir de 5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **6** como se muestra en el Esquema 3.

Esquema 3



*Paso 1 – Preparación de 3-yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**8**):*

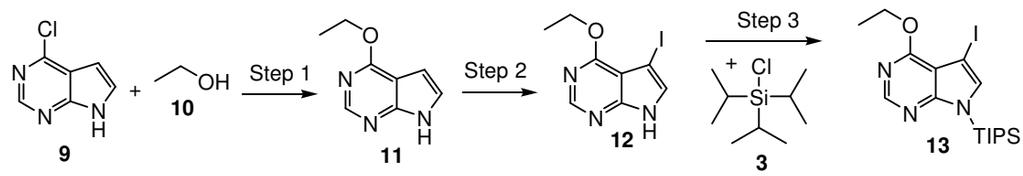
[0628] 5-Metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**6**, 1.1 g, 3.8 mmol) y 10 mL de diclorometano se combinan en un matraz de fondo redondo y se agitan por 10 minutos. Se añade una lechada de N-yodosuccinimida (1.0 g, 4.6 mmol) en

5 mL de diclorometano y se agita a temperatura ambiente toda la noche. La reacción se extingue con tiosulfato de sodio (20 mL, 1M en agua) y la capa acuosa se extrae con acetato de etilo. La capa orgánica combinada se lava con agua y salmuera, se seca con sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con acetato de etilo y hexanos. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado como un aceite amarillo claro (**8**, 1.2 g, 75%). MS (ESI) $[M+H^+]^+ = 415.08$.

Ejemplo 4: Síntesis de 4-etoxi-5-yodo-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina 13.

[0629] 4-Etoxi-5-yodo-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina **13** se prepara en tres Pasos a partir de 4-cloro-7H-pirrolo[2,3-d]pirimidina **9** como se muestra en el Esquema 4.

Esquema 4



*Paso 1 – Preparación de 4-etoxi-7H-pirrolo[2,3-d]pirimidina (**11**):*

[0630] 4-Cloro-7H-pirrolo[2,3-d]pirimidina (**9**, 300 mg, 1.95 mmol) se combina con 3.00 mL de etanol (**10**, 51.4 mmol), luego se añade hidróxido de potasio (0.226 g, 4.03 mmol). La reacción se calienta a 120 ^oC por 3 horas en un microondas, luego se extrae con acetato de etilo y cloruro de amonio saturado acuoso. La capa orgánica se lava con salmuera, se seca con sulfato de magnesio, se filtra y el filtrado

se concentra bajo vacío. El material resultante se recristaliza a partir del metanol para proporcionar el compuesto deseado(**11**, 213 mg). MS (ESI) $[M+H^+]^+ = 164.9$.

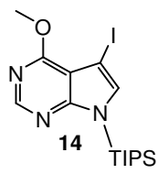
*Paso 2 – Preparación de 4-etoxi-5-yodo-7H-pirrolo[2,3-d]pirimidina (**12**):*

[0631] **A** 4-etoxi-7H-pirrolo[2,3-d]pirimidina (**11**, 1.60 g, 9.8 mmol) se añade 50.0 mL de diclorometano, N,N-dimetilformamida (2.0 mL, 26 mmol) y N-yodosuccinimida (2.40 g, 10.7 mmol) y la reacción se agita a temperatura ambiente por 2 horas. La reacción se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca con sulfato de sodio, se filtra y el filtrado se concentra bajo vacío para proporcionar el compuesto deseado(**12**, 2.70 g).

*Paso 3 – Preparación de 4-etoxi-5-yodo-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina (**13**):*

[0632] **A** 4-etoxi-5-yodo-7H-pirrolo[2,3-d]pirimidina (**12**, 2.70 g, 9.34 mmol) en 60.0 mL de tetrahidrofurano bajo una atmósfera de nitrógeno, se añade hidruro de sodio (411.0 mg, 10.27 mmol). La reacción se agita a temperatura ambiente por 20 minutos, luego se añade cloruro de triisopropilsilil (**3**, 2.177 mL, 10.27 mmol). La reacción se agita a temperatura ambiente por 2 horas, luego se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 5-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**13**, 3.90 g).

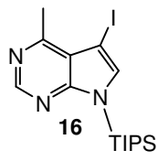
[0633] 5-Yodo-4-metoxi-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina **14**



14

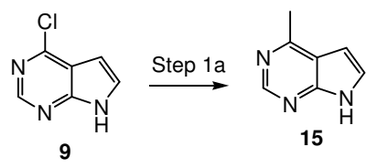
se prepara de forma similar al protocolo del Esquema 4, reemplazando el etanol con metanol en el Paso 1.

[0634] 5-Yodo-4-metil-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina **16**



16

se prepara de forma similar al protocolo del Esquema 4, donde el Paso 1 es Reemplazado por el siguiente Paso 1a:



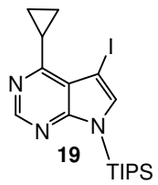
9 **15**

*Paso 1a – Preparación de 4-metil-7H-pirrolo[2,3-d]pirimidina (**15**):*

[0635] **A** 4-cloro-7H-pirrolo[2,3-d]pirimidina (**9**, 5.03 g, 32.8 mmol) en 100 mL de tolueno, se añade complejo de [1,1'-bes(diel fenilfosfino)ferroceno]dicloropaladio(II) 1:1 con diclorometano (0.627 g, 0.328 mmol) bajo una atmósfera de nitrógeno. Después de agitar por 10 minutos, se añade lentamente bromuro de metilmagnesio (62.9 mL, 3.00 M in eter, 189 mmol). La reacción se calienta a 55 ^{o}C toda la noche, luego se enfría a -70 a -80 ^{o}C y se extingue al añadir cloruro de amonio gota a gota. Luego se añade ácido clorhídrico 1N y sel pH se ajusta a 7-8 con la adición de bicarbonato de sodio saturado. Luego

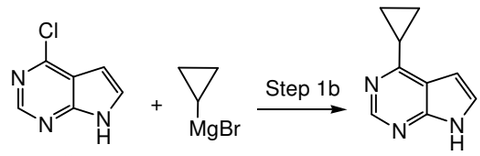
se extrae 3 veces con acetato de etilo. La capa orgánica combinada se lava con cloruro de amonio saturado y salmuera, luego se seca con sulfato de magnesio, se filtra y el filtrado se concentra bajo vacío. El material resultante se purifica median cromatografía de columna de gel de silicio, eluyendo con acetato de etilo y diclorometano, ten metanol y diclorometano. Las fracciones apropiadas se combinan y se concentran bajo vacío para proporcionar el compuesto deseado como un sólido (**15**). MS (ESI) $[M+H^+]^+$ = 134. Éste se hace reacciónar de forma similar a los Pasos 2 y 3 del Esquema 4 para proporcionar el compuesto deseado **16**.

[0636] 4-Ciclopropil-5-yodo-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina **19**



19

se prepara de forma similar al protocolo del Esquema 4, donde el Paso 1 es Reemplazado por el siguiente Paso 1b:



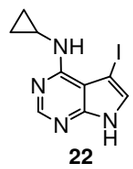
9 **17** **18**

*Paso 1b – Preparación de 4-ciclopropil-7H-pirrolo[2,3-d]pirimidina (**18**):*

[0637] Se combinan 4-Cloro-7H-pirrolo[2,3-d]pirimidina (**9**, 0.452 g, 2.94 mmol), bromuro de ciclopropilmagnesio (**17**, 31.4 mL, 0.50 M en tetrahidrofurano, 15.7 mmol), y complejo [1,1'-bes(diel fenilfosfino)ferroceno]dicloropaladio(II) 1:1 con diclorometano (0.240 g, 0.294 mmol) con 15.4 mL de tolueno. La reacción se calienta a 60 ^oC toda la noche, luego se extingue con 1 M de ácido clorhídrico acuoso de pH 4 y se filtra a través de un lecho de celita. Se separan las capas del

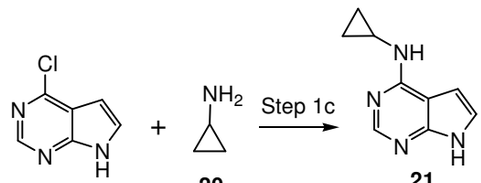
filtrado y la capa acuosa se extrae con acetato de etilo. Las capas orgánicas combinadas se lavan con salmuera, se secan en sulfato de sodio, se filtran y el filtrado se concentra bajo vacío. El material resultante es purificado mediante cromatografía de columna de gel de silicio, eluyendo con acetato de etilo y hexano. Las fracciones apropiadas se combinan y se concentran bajo vacío para proporcionar el compuesto deseado (**18**, 0.465 g). MS (ESI) $[M+H^+]^+$ = 160.1. Éste se hace reacciónar de forma similar a los Pasos 2 y 3 del Esquema 4 para proporcionar el compuesto deseado **19**.

[0638] Ciclopropil-(5-yodo-7H-pirrolo[2,3-d]pirimidina-4-il)-amino **22**



22

se prepara de forma similar al protocolo del Esquema 4, Pasos 1 y 2, donde el Paso 1 es Reemplazado por el siguientePaso 1c:



9 **20** **21**

*Paso 1c – Preparación de ciclopropil-(7H-pirrolo[2,3-d]pirimidin-4-il)-amino (**21**):*

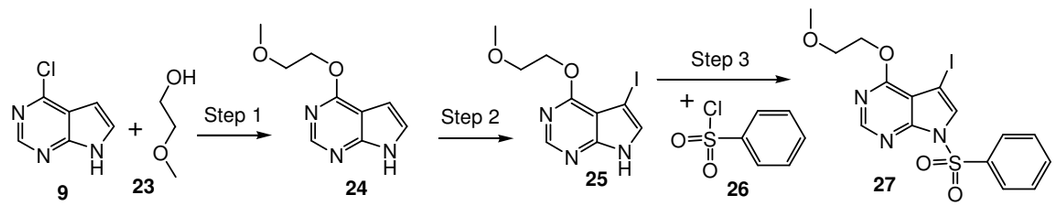
[0639] Se disuelve 4-Cloro-7H-pirrolo[2,3-d]pirimidina (**9**, 1.06 g, 6.90 mmol) en ciclopropilamina (**20**, 2.42 mL, 34.5 mmol) y se calienta hasta reflujo toda la noche. La mezcla de reacción se enfría y se vierte en agua, luego se extrae con acetato de etilo. La capa orgánica se lava con salmuera, se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con acetato de etilo y

diclorometano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**21**, 337 mg). MS (ESI) $[M+H^+]^+$ = 174.9. Éste se hace reacciónar de forma similar a los Paso 2 del Esquema 4 para proporcionar el compuesto deseado**22**.

Ejemplo 5: Síntesis de 7-bencenosulfonil-5-yodo-4-(2-metoxi-etoxi)-7H-pirrolo[2,3-d]pirimidina 27.

[0640] 7-Bencenosulfonil-5-yodo-4-(2-metoxi-etoxi)-7H-pirrolo[2,3-d]pirimidina **27** se prepara en tres Pasos a partir de 4-cloro-7H-pirrolo[2,3-d]pirimidina **9** como se muestra en el Esquema 5.

Esquema 5



*Paso 1 – Preparación de4-(2-metoxi-etoxi)-7H-pirrolo[2,3-d]pirimidina (**24**):*

[0641] **A** 4-Cloro-7H-pirrolo[2,3-d]pirimidina (**9**, 5.00 g, 32.6 mmol) en 12.5 mL de 2-metoxi-etanol (**23**, 158 mmol), se añade hidróxido de potasio (3.3 g, 59 mmol). La reacción se calienta a 100 ^oC toda la noche, luego se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca con sulfato de sodio, se filtra y el filtrado se concentra bajo vacío para proporcionar el compuesto deseado(**24**, 5.70 g).

*Paso 2 – Preparación de5-yodo-4-(2-metoxi-etoxi)-7H-pirrolo[2,3-d]pirimidina (**25**):*

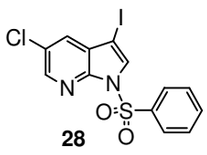
[0642] **A** 4-(2-metoxi-etoxi)-7H-pirrolo[2,3-d]pirimidina (**24**, 5.70 g, 29.5 mmol) en 150.0 mL de diclorometano, se añaden N,N-dimetilformamida (6.0 mL, 78 mmol) y N-yodosuccinimida (7.22 g, 32.1 mmol) y la reacción se agita a temperatura ambiente por 2 horas. La reacción se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca con sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. El material resultante se lava con acetato de etilo y hexano para proporcionar el compuesto deseado(**25**, 6.75 g).

*Paso 3 – Preparación de7-bencenosulfonil-5-yodo-4-(2-metoxi-etoxi)-7H-pirrolo[2,3-d]pirimidina (**27**):*

[0643] **A** 5-yodo-4-(2-metoxi-etoxi)-7H-pirrolo[2,3-d]pirimidina (**25**, 3.67 g, 11.5 mmol) en 60.0 mL de tetrahidrofurano bajo una atmósfera de nitrógeno, se añade hidruro de sodio (506.0 mg, 12.65 mmol). La reacción se agita a temperatura ambiente por 20 minutos, luego se añade cloruro de bencenosulfonil (**26**, 1.614 mL, 12.65 mmol). La reacción se agita a temperatura ambiente por 30 minutos, luego se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 15-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**27**, 4.50 g). MS (ESI) $[M+H^+]^+ = 460.0$.

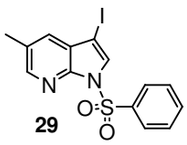
[0644] 1-Bencenosulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **28**, 1-bencenosulfonil-3-yodo-5-metil-1H-pirrolo[2,3-b]piridina **29**, y 7-

bencenosulfonil-4-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidina **30**,



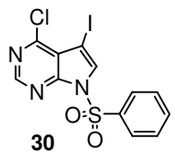
28

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29

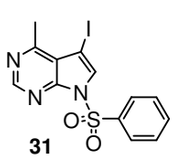
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30

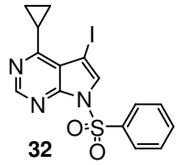
se preparan siguiendo el protocolo del Esquema 5 Paso 3 o Pasos 2 y 3, reemplazando 5-yodo-4-(2-metoxi-etoxi)-7H-pirrolo[2,3-d]pirimidina **25** con 5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **2** y 3-yodo-5-metil-1H-pirrolo[2,3-b]piridina **7**, respectivamente en Paso 3, o al reacciónar 4-cloro-7H-pirrolo[2,3-d]pirimidina **9** directamente en el Paso 2.

[0645] 7-Bencenosulfonil-5-yodo-4-metil-7H-pirrolo[2,3-d]pirimidina **31** y 7-bencenosulfonil-4-ciclopropil-5-yodo-7H-pirrolo[2,3-d]pirimidina **32**,



31

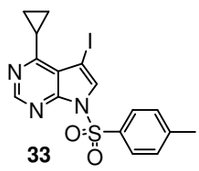
y



32

se preparan siguiendo el protocolo del Esquema 5 Pasos 2 y 3, reemplazando 4-(2-metoxi-etoxi)-7H-pirrolo[2,3-d]pirimidina **24** con 4-metil-7H-pirrolo[2,3-d]pirimidina **15** y 4-ciclopropil-7H-pirrolo[2,3-d]pirimidina **18**, respectivamente, en el Paso 2.

[0646] 4-Ciclopropil-5-yodo-7-(tolueno-4-sulfonil)-7H-pirrolo[2,3-d]pirimidina **33,**



33

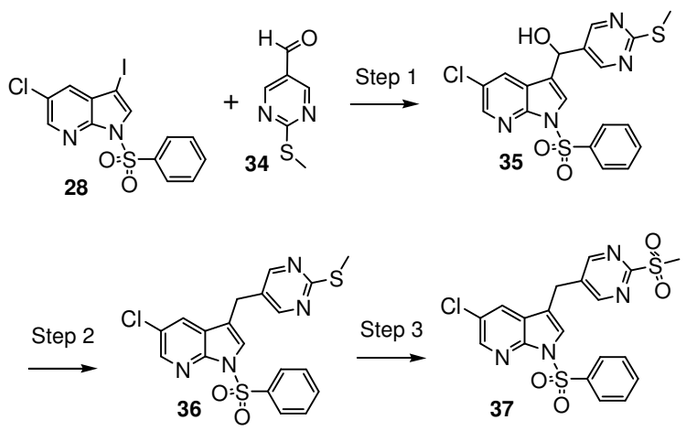
se sintetiza de forma similar al compuesto **32**, donde 4- cloruro de

metilbencenosulfonil se usa en lugar del cloruro de bencenosulfonil **26** en el Paso 3 del Esquema 5.

Ejemplo 6: Síntesis de 1-bencenosulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina 37.

[0647] 1-bencenosulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina **37** se prepara en tres Pasos a partir de 1-bencenosulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **28** y 2-metilsulfanil-pirimidina-5-carbaldehído**34** como se muestra en el Esquema 6.

Esquema 6



*Paso 1 – Preparación de(1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridina-3-il)-(2-metilsulfanil-pirimidin-5-il)-metanol (**35**):*

[0648] A una solución de 1-bencenosulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina (**28**, 8.40 g, 20.1 mmol) en 96.3 mL de tetrahidrofurano a -40 ^{o}C bajo nitrógeno, se añade lentamente cloruro de isopropilmagnesio (10.1 mL, 2.0 M en tetrahidrofurano, 20.3 mmol). La reacción se deja calentar a 5 ^{o}C por 60 minutos, luego se enfría a -40 ^{o}C, seguida por la adición de 2-metilsulfanil-pirimidina-5-carbaldehído(**34**, 2.50 g, 16.2 mmol) en 15.0 mL de tetrahidrofurano. La reacción se

deja calentar a 10 ^{o}C por 2 horas, luego se vierte en cloruro de amonio acuoso y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y elfiltrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio eluyendo con 40-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y los solventes se remueven bajo vacío para proporcionar el compuesto deseado como un sólido blanco (**35**, 4.0 g). MS (ESI) $[M+H^{+}]^{+}$ = 447.2.

*Paso 2 – Preparación de1-bencenosulfonil-5-cloro-3-(2-metilsulfanil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**36**):*

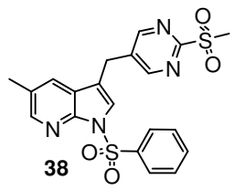
[0649] **A** (1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridina-3-il)-(2-metilsulfanil-pirimidin-5-il)-metanol (**35**, 4.70 g, 10.5 mmol) en 120.0 mL de acetonitrilo, se añaden trietilsilano (22.0 mL, 138 mmol) y ácido trifluoroacético (11.0 mL, 143 mmol). La reacción se agita a 80 ^{o}C por 3 horas, luego se concentra bajo vacío, se mezcla con carbonato de potasio acuoso y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y los solventes se remueven bajo vacío para proporcionar el compuesto deseado(**36**, 2.90 g).

*Paso 3 – Preparación de1-bencenosulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**37**):*

[0650] **A** 1-bencenosulfonil-5-cloro-3-(2-metilsulfanil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**36**, 4.40 g, 10.2 mmol) en 100.0 mL de diclorometano, se añade ácido meta-cloroperoxibenzoico (max. 77%, 4.90 g, 21.9 mmol) a 0 ^{o}C. La

reacción se agita a 0 °C por 40 minutos, luego se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra, y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio eluyendo con 20% acetato de etilo en hexano. Las fracciones apropiadas se combinan y los solventes se remueven bajo vacío para proporcionar el compuesto deseado(**37**, 3.76 g). MS (ESI) $[M+H^+]^+ = 463.0$.

[0651] 1-Bencenosulfonil-3-(2-metanosulfonil-pirimidin-5-ilmetil)-5-metil-1H-pirrolo[2,3-b]piridina **38**



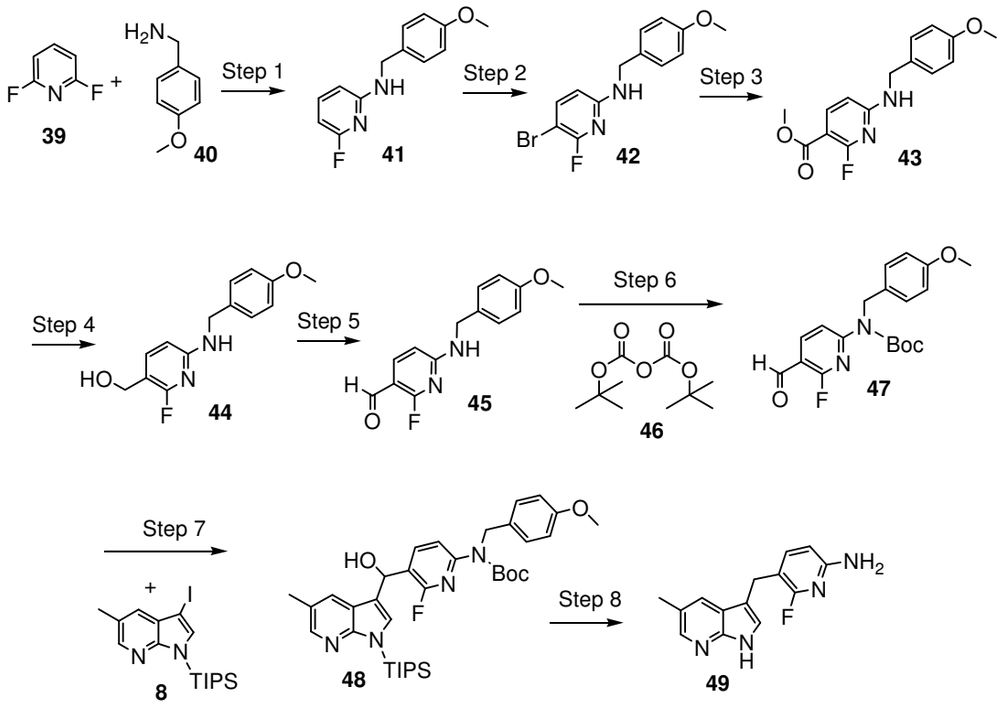
38

se prepara siguiendo el protocolo del Esquema 6, reemplazando 1-bencenosulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **28** con 1-bencenosulfonil-3-yodo-5-metil-1H-pirrolo[2,3-b]piridina **29** en el Paso 1.

Ejemplo 7: Síntesis de 6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-ilamina 49.

[0652] 6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-ilamina **49** se prepara en siete Pasos a partir de 2,6-difluoro-piridina **39** y 4-metoxi-benzilamina **40** como se muestra en el Esquema 7.

Esquema 7



*Paso 1 – Preparación de(6-fluoro-piridina-2-il)-(4-metoxi-benzil)-amino (**41**):*

[0653] **A** 2,6-difluoro-piridina (**39**, 100 g, 869 mmol) en 500 mL de N-metilpirrolidinona, se añaden 4-metoxi-benzilamina (**40**, 136 mL, 1.043 mol) y N,N-diisopropiletilamina (304 mL, 1.738 mol). La reacción se agita a 90 ^{o}C toda la noche, luego se vierte en 8 L de agua. El precipitado resultante se recolecta por filtración y se lava con agua, luego se saca en acetato de etilo y se lava con agua. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. El material resultante se tritura con heptano y se recolecta por filtración para proporcionar el compuesto deseado(**41**, 151 g, 650 mmol, 74.8 % rendimiento).

*Paso 2 – Preparación de(5-bromo-6-fluoro-piridina-2-il)-(4-metoxi-benzil)-amino (**42**):*

[0654] A (6-fluoro-piridina-2-il)-(4-metoxi-benzil)-amino (**41**, 151 g, 650 mmol) en 4 L de acetonitrilo bajo una atmósfera de nitrógeno, se añade en porciones N-

bromosuccinimida (116 g, 650 mmol). Después de reacciónar por 2 horas, el solvente se remueve bajo vacío y el residuo se saca en acetato de etilo, luego se vierte en tiosulfato de sodio acuoso. La capa orgánica se lava con agua tibia de salmuera, se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. El material resultante se cristaliza a partir de heptano para proporcionar el compuesto deseado(**42**, 172 g, 553 mmol, 85 % rendimiento).

*Paso 3 – Preparación de 2-fluoro-6-(4-metoxi-benzilamino)-éster metilo de ácido nicotínico(**43**):*

[0655] A (5-bromo-6-fluoro-piridina-2-il)-(4-metoxi-benzil)-amino (**42**, 85 g, 273 mmol) en 1.5 L de metanol en un frasco Parr de 2 L, se añaden trietilamina (77 mL, 546 mmol) y [1,1'-bis(difenilfosfino)ferroceno] dicloropaladio(II) (5.80 g, 7.10 mmol). La reacción se calienta a 100 ^{o}C bajo 100 psi de monóxido de carbono toda la noche. La reacción se enfría y se filtra a través de celita y el filtrado se concentra bajo vacío. El material resultante se disuelve en diclorometano y se pasa a través de un tapón de gel de silicio, eluyendo con acetato de etilo. El solvente se remueve bajo vacío para proporcionar el compuesto deseado como un sólido color melocotón (**43**, 70 g, 241 mmol, 88 % rendimiento).

*Paso 4 – Preparación de[2-fluoro-6-(4-metoxi-benzilamino)-piridina-3-il]-metanol (**44**):*

[0656] **A**2-fluoro-6-(4-metoxi-benzilamino)-éster metilo de ácido nicotínico(**43**, 70 g, 241 mmol) en 350 mL de tetrahidrofurano, se añade hidruro de aluminio y litio (362 mL, 1 M en tetrahidrofurano, 362 mmol) gota a gota mientras se enfría. La reacción se agita a temperatura ambiente por 2 horas, luego se extingue con adición gota a gota de 14 mL de agua, 14 mL de hidróxido de sodio acuoso al 15%, y 42 mL

de agua, secuencialmente. Luego se añaden 500 mL de éter metil tert-butílico y los sólidos se remueven por filtración. El filtrado se concentra bajo vacío y el sólido resultante se disuelve en diclorometano, se pasa a través de un tapón de gel de silicio y se eluye con 50-100% de acetato de etilo en heptano. El solvente se remueve bajo vacío para proporcionar el compuesto deseado como un sólido blanco (**44**, 63 g, 240 mmol, 100 % rendimiento).

*Paso 5 – Preparación de2-fluoro-6-(4-metoxi-benzilamino)-piridina-3-carbaldehído(**45**):*

[0657] A [2-fluoro-6-(4-metoxi-benzilamino)-piridina-3-il]-metanol (**44**, 63 g, 240 mmol) en 1.25 L de acetato de etilo, se añade óxido de manganeso(IV) (210 g, 2.416 mol). La reacción se agita toda la noche a temperatura ambiente, luego se filtra a través de celita y la celita se enjuaga con acetato de etilo. Los filtrados combinados se concentran bajo vacío y la el sólido resultante se tritura con heptano y se recolecta por filtración para proporcionar el compuesto deseado como un sólido blanco (**45**, 62 g, 238 mmol, 99% rendimiento).

*Paso 6 – Preparación de(6-fluoro-5-formil-piridina-2-il)-(4-metoxi-benzil)-éter terbutílico de ácido carbámico (**47**):*

[0658] Se combinan 2-Fluoro-6-(4-metoxi-benzilamino)-piridina-3-carbaldehído(**45**, 62 g, 238 mmol), 600 mL de alcohol tert-butílico, di-tert-butildicarbonaA (**46**, 83 mL, 357 mmol) y dimetilaminopiridina (2.91 g, 23.82 mmol) en un matraz de fondo redondo. La reacción se agita a 30 ^{o}C toda la noche y se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 0-20% acetato de etilo en hexano. Las

fracciones apropiadas se combinan y los solventes se remueven bajo vacío para proporcionar el compuesto deseado(**47**, 54 g, 150 mmol, 62.9 % rendimiento).

*Paso 7 – Preparación de{6-fluoro-5-[hidroxi-(5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina-3-il)-metil]-piridina-2-il}-(4-metoxi-benzil)-éter terbutílico de ácido carbámico (**48**):*

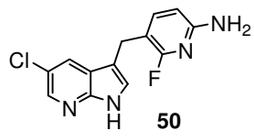
[0659] A 3-yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**8**, 40 g, 97.0 mmol) en 400 mL de tetrahidrofurano bajo una atmósfera de nitrógeno a -20 ^{o}C, se añade cloruro de isopropilmagnesio (54.8 mL, 2 M en tetrahidrofurano, 110 mmol) y la reacción se deja calentar a 0 ^{o}C por 30 minutos. La reacción se enfría a -40 ^{o}C y se añade (6-fluoro-5-formil-piridina-2-il)-(4-metoxi-benzil)-éter terbutílico de ácido carbámico (**47**, 15.81 g, 43.9 mmol) en tetrahidrofurano. La reacción se deja calentar a 0 ^{o}C por 1 hora, luego se extingue con salmuera y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 0-40% acetato de etilo en hexano. Las fracciones apropiadas se combinan y los solventes se remueven bajo vacío para proporcionar el compuesto deseado(**48**, 21 g, 32.4 mmol, 73.8 % rendimiento).

*Paso 8 – Preparación de6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-ilamina (**49**):*

[0660] A {6-fluoro-5-[hidroxi-(5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina-3-il)-metil]-piridina-2-il}-(4-metoxi-benzil)-éter terbutílico de ácido carbámico (**48**, 21 g, 32.4 mmol) en 500 mL de acetonitrilo, se añaden trietilsilano (51.7 mL, 324 mmol) y ácido trifluoroacético (24.93 mL, 324 mmol). La reacción se agita a 50 ^{o}C por varias horas, luego se concentra bajo vacío, y el residuo se saca

en 250 mL de diclorometano y se añaden 250 mL de ácido trifluoroacético. La mezcla se agita hasta reflujo por varias horas, luego se concentra bajo vacío. El residuo se saca en acetato de etilo y se vierte en carbonato de potasio acuoso. La capa orgánica se separa, se concentra bajo vacío y se purifica por cromatografía de columna de gel de silicio, eluyendo con 0-5% metanol en diclorometano. Las fracciones apropiadas se combinan y los solventes se remueven bajo vacío para proporcionar el compuesto deseado(**49**, 5.2 g, 20.29 mmol, 62.7 % rendimiento).

[0661] 5-(5-Cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-6-fluoro-piridina-2-ilamina **50**



50

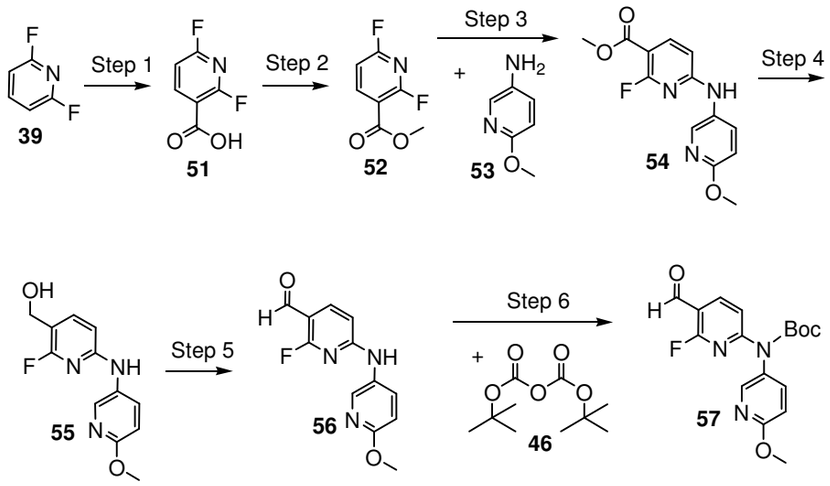
se prepara siguiendo el protocolo del Esquema 7, reemplazando 3-yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **8** con 5-cloro-3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **4** en el Paso 7.

Ejemplo 8: Síntesis de reactivos aldehídos.

[0662] Los reactivos aldehídos que se usan al hacer compuestos se preparan de acuerdo con los siguientes protocolos. En estas reacciónes, el aldehído desprotegido se aisla después del Paso 5, o el aldehído Boc-protegido puede usarse en la Preparación de los compuestos.

[0663] (6-etoxi-piridina-3-il)-(6-fluoro-5-formil-piridina-2-il)-éter terbutílico de ácido carbámico **57** se prepara en seis Pasos a partir de 2,6-difluoro-piridina **39** como se muestra en el Esquema 8.

Esquema 8



*Paso 1 – Preparación de2,6-difluoro-ácido niconítico (**51**):*

[0664] En un matraz de fondo redondo, a 2,6-difluoro-piridina (**39**, 7.10 g, 61.7 mmol) en 150.0 mL de tetrahidrofurano bajo una atmósfera de nitrógeno a -78 ^{o}C, se añade lentamente n-butillitio (26.0 mL, 2.50 M en hexano, 65.0 mmol). Después de 30 minutos, se añaden 3.0 g de hielo seco y 1 hora después la reacción se deja calentar a temperatura ambiente. La reacción se vierte en agua, se extrae con acetato de etilo y la capa acuosa se ajusta a pH 4-5 con ácido clorhídrico1 N. Éste se extrae con acetato de etilo y la capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío para proporcionar el compuesto deseado(**51**, 5.6 g).

*Paso 2 – Preparación de2,6-difluoro-éster metilo de ácido nicotínico(**52**):*

[0665] En un matraz de fondo redondo, se combinan 2,6-difluoro-ácido niconítico (**51**, 5.60 g, 35.2 mmol), 60.0 mL de metanol y ácido sulfúrico (1.0 mL, 19.0 mmol) y se calienta hasta reflujo toda la noche. La reacción se vierte en agua, se ajusta a pH 9 con carbonato de potasio acuoso 1M, y se extrae con acetato de etilo. La capa

orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío para proporcionar el compuesto deseado como un aceite amarillo (**52**, 3.5 g).

*Paso 3 – Preparación de 2-fluoro-6-(6-metoxi-piridina-3-ilamino)-éster metilo de ácido nicotínico(**54**):*

[0666] En un matraz de fondo redondo, se combina 2,6-difluoro-éster metilo de ácido nicotínico(**52**, 2.00 g, 11.6 mmol) con 20.0 mL de N,N-dimetilformamida bajo una atmósfera de nitrógeno at -40 ^{o}C. A esto se añade , 5-amino-2-metoxipiridina (**53**, 1.55 g, 12.5 mmol) y trietilamina (5.0 mL, 36.0 mmol) y la reacción se agita a -40 ^{o}C, luego se calienta a temperatura ambiente y se deja en reacción toda la noche. La reacción se calienta a 50 ^{o}C por el fin de semana, luego a 70 ^{o}C por 3 horas. La reacción se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**54**, 1.20 g).

*Paso 4 – Preparación de[2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-metanol (**55**):*

[0667] **A** 2-fluoro-6-(6-metoxi-piridina-3-ilamino)-éster metilo de ácido nicotínico(**54**, 1.20 g, 4.33 mmol) en 50.0 mL de tetrahidrofurano, se añade tetrahidroaluminato de litio (8.66 mL, 1.00 M en tetrahidrofurano, 8.66 mmol) y la reacción se agita a temperatura ambiente por 3 horas. Se añade sulfato de sodio decahidratado (5g) y después de 1 hora, la reacción se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio eluyendo con 20-100% acetato de etilo en hexano. Las

fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**55**, 700 mg). MS (ESI) $[M+H^+]^+$ = 250.1.

*Paso 5 – Preparación de 2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-carbaldehído(**56**):*

[0668] A [2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-metanol (**55**, 0.700 g, 2.81 mmol) en 20.0 mL de tetrahidrofurano, se añade Dess-Martin periodinano (1.44 g, 3.40 mmol) y la reacción se agita a temperatura ambiente por 30 minutos. La reacción se vierte en carbonato de potasio acuoso y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**56**, 450 mg). MS (ESI) $[M+H^+]^+$ = 248.0.

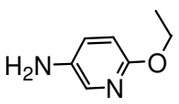
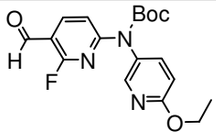
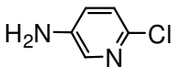
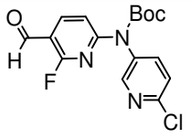
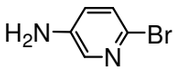
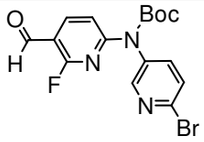
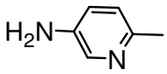
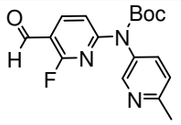
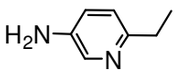
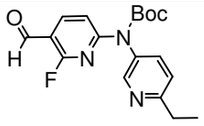
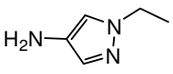
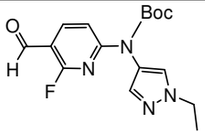
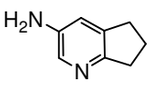
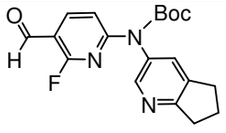
*Paso 6 – Preparación de (6-fluoro-5-formil-piridina-2-il)-(6-metoxi-piridina-3-il)-éter terbutílico de ácido carbámico (**57**):*

[0669] A 2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-carbaldehído(**56**, 2.21 g, 8.94 mmol) en 50 mL de tetrahidrofurano, se añaden di-tert-butildicarbonaA (**46**, 2.82 g, 12.9 mmol) y 4-dimetilaminopiridina (0.30 g, 2.4 mmol) y la reacción se agita a temperatura ambiente toda la noche. La reacción se concentra bajo vacío y luego, el material resultante se purifica por cromatografía de columna de gel de silicio eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**57**, 1.39 g).

[0670] Los aldehídos adicionales se preparan de forma similar al protocolo del

Esquema 8, como se muestra en el la siguiente tabla, reemplazando 5-amino-2-metoxipiridina **53** con un compuesto amino apropiado en el Paso 3. Mientras la tabla índica el aldehído Boc-protegido, se puede aislar el aldehído no Boc protegido después del Paso 5.

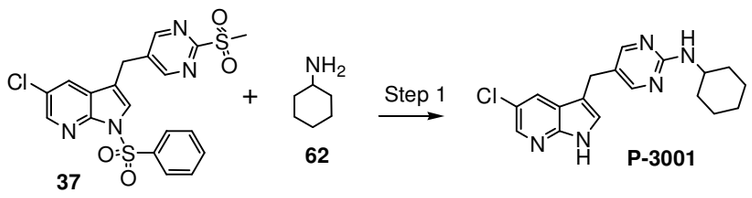
Tabla 3

Paso 3 Compuesto amino	Aldehído Final
	
	
	
	
	
	
	

Ejemplo 9: Síntesis de [5-(5-cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidin-2-il]-ciclohexil-aminoP-3001.

[0671] [5-(5-Cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidin-2-il]-ciclohexil-amino **P-3001** se prepara en un paso a partir de 1-bencenosulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina **37** y ciclohexanamina **62** como se muestra en el Esquema 9.

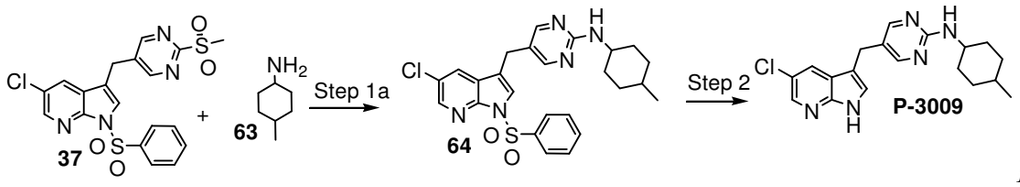
Esquema 9



*Paso 1 – Preparación de [5-(5-cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidin-2-il]-ciclohexil-amino (**P-3001**):*

[0672] En un frasco para microondas, a 1-bencenosulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**37**, 60 mg, 0.13 mmol) en 1.0 mL de N-metilpirrolidinone, se añade ciclohexanamina (**62**, 0.20 g, 2.0 mmol). La reacción se calienta a 155 ^{o}C por 25 minutos en un microondas, luego se añade hidróxido de potasio (1.0 mL, 1.00 M en agua, 1.0 mmol) la reacción se calienta a 95 ^{o}C por 15 minutos en un microondas. La reacción se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se recolectan y se concentran bajo vacío para proporcionar el compuesto deseado(**P-3001**, 11.4 mg). MS (ESI) $[M+H^{+}]^{+}$ = 341.9.

[0673] [5-(5-Cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidin-2-il]-(4-metil-ciclohexil)-amino **P-3009** se preparó de forma similar al Esquema 9, reemplazando Paso 1 con los siguientes Pasos 1a y 2:



*Paso 1a – Preparación de [5-(1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidin-2-il]-(4-metil-ciclohexil)-amino (**64**):*

[0674] En un frasco para microondas, a 1-bencenosulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**37**, 0.140 g, 0.302 mmol) en 2.0 mL de N-metilpirrolidinona, se añade 4-metilciclohexilamina (**63**, 0.30 g, 2.6 mmol). La reacción se calienta a 160 ^{o}C por 20 minutos en un microondas, luego se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**64**, 0.120 g). MS (ESI) $[M+H^{+}]^{+}$ = 496.4.

*Paso 2 – Preparación de[5-(5-cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidin-2-il]-(4-metil-ciclohexil)-amino (**P-3009**):*

[0675] **A** [5-(1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidin-2-il]-(4-metil-ciclohexil)-amino (**64**, 0.120 g, 0.242 mmol) en 5.0 mL de tetrahidrofurano, se añade tetrabutilamonio fluoruro trihidraA (0.20 g, 0.63 mmol). La reacción se agita a temperatura ambiente toda la noche, luego se vierte en agua y

se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se recolectan y se concentran bajo vacío para proporcionar el compuesto deseado(**P-3009**, 1.4 mg). MS (ESI) $[M+H^+]^+$ = 355.95.

[0676] Los compuestos se preparan siguiendo el protocolo del Esquema 9. Los compuestos se realizan sustituyendo ciclohexanamina **62** con un amino apropiado y sustituyendo opcionalmente 1-bencenosulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina **37** con 1-bencenosulfonil-3-(2-metanosulfonil-pirimidin-5-ilmetil)-5-metil-1H-pirrolo[2,3-b]piridina **38**.

Los siguientes compuestos se realizan usando este procedimiento: [5-(5-Cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-ciclopentil-amino (**P-3051**),
[5-(5-Cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-(4,4-diflúoro-ciclohexil)-amino (**P-3052**),
[5-(5-Cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-ciclopropil-amino (**P-3005**),
[5-(5-Cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-cicloheptil-amino (**P-3006**),
[5-(5-Cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-ciclobutil-amino (**P-3007**),
(4-Fluoro- fenil)-[5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-amino (**P-3010**),
(4-Cloro- fenil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidina-2-il]-

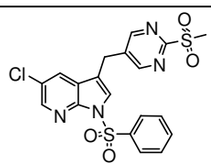
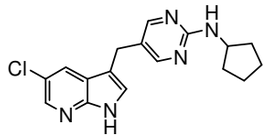
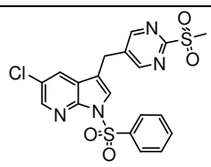
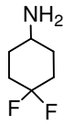
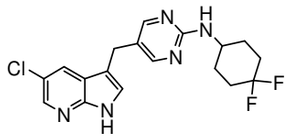
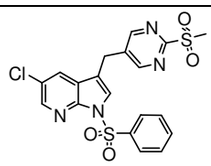
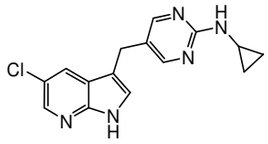
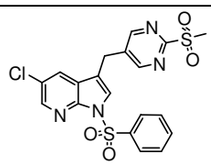
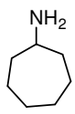
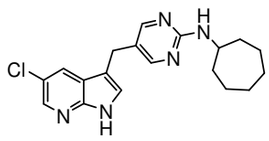
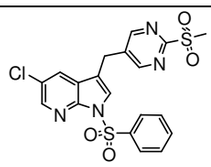
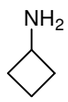
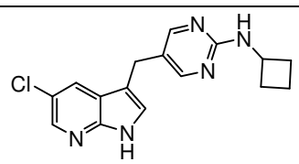
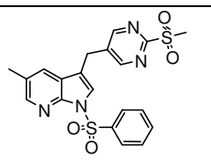
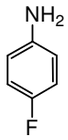
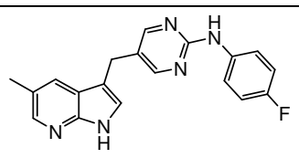
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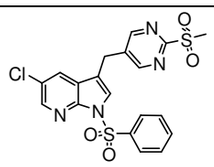
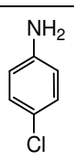
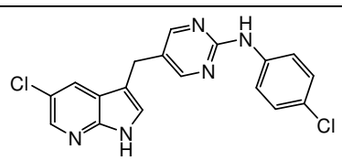
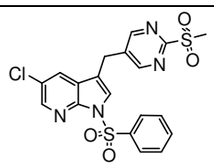
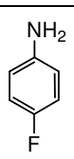
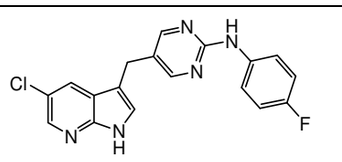
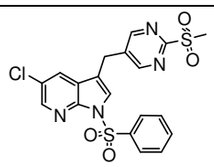
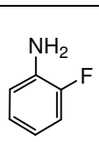
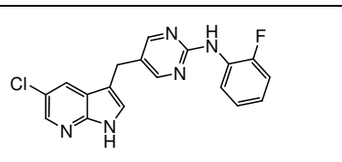
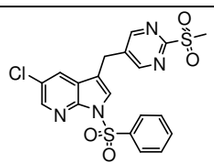
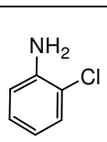
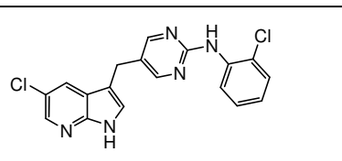
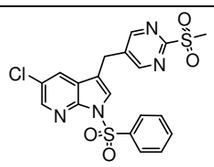
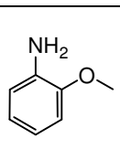
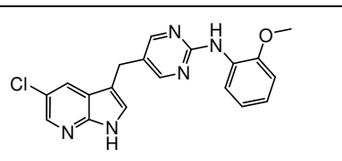
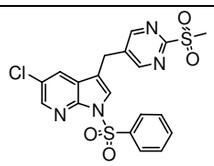
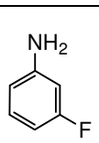
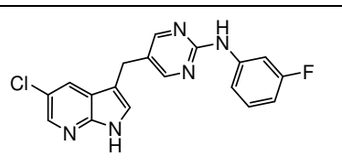
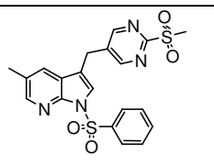
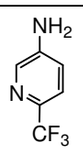
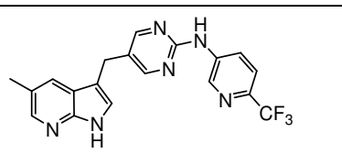
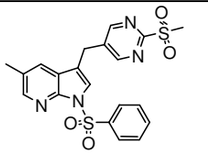
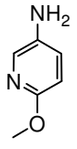
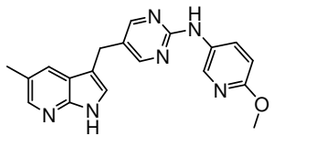
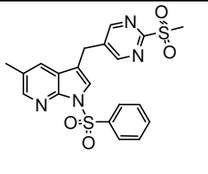
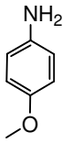
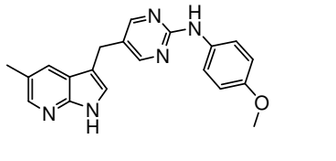
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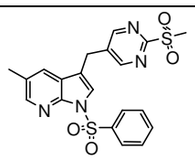
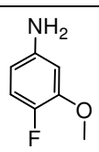
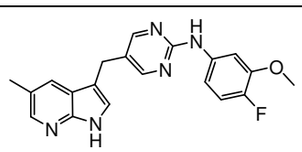
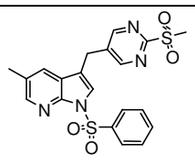
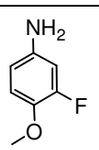
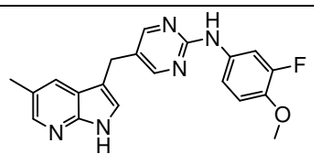
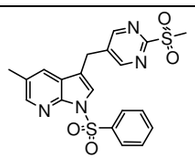
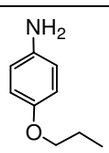
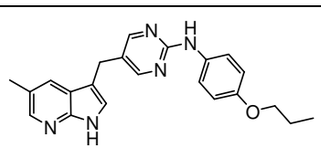
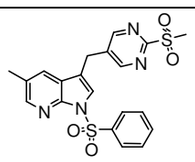
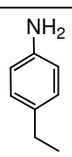
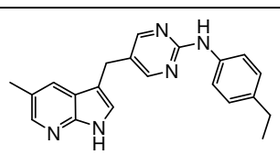
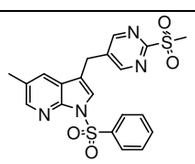
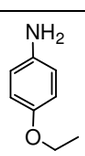
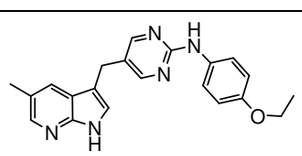
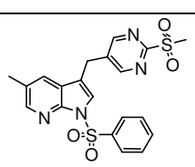
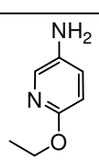
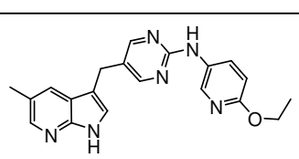
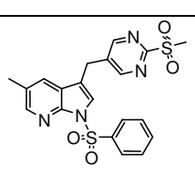
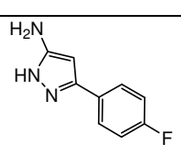
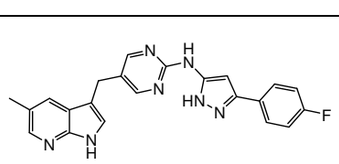
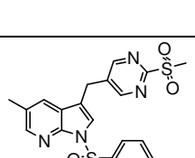
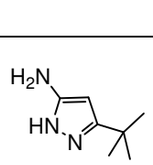
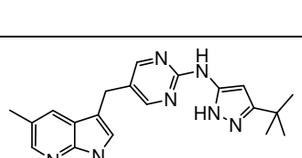
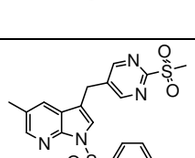
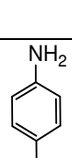
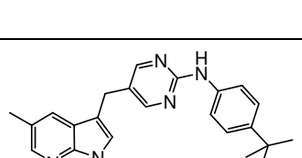
Los siguientesTabla indicatos te 2-metanosulfonil-pirimidina-5-ilmetil)-1H-

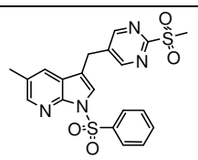
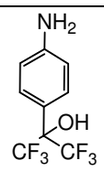
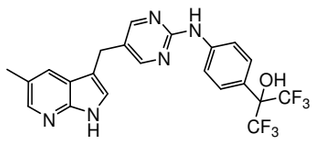
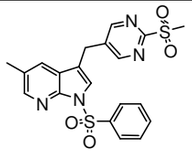
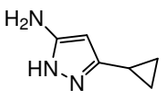
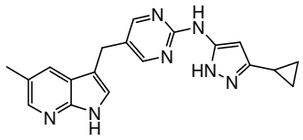
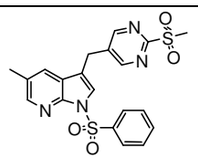
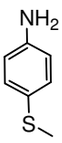
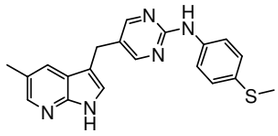
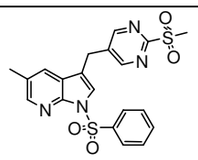
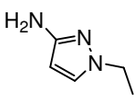
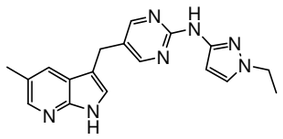
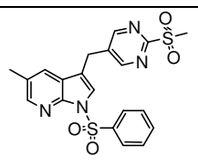
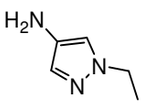
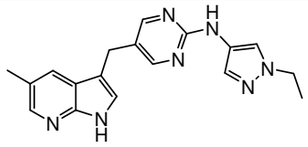
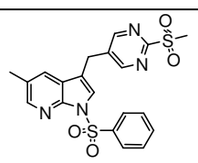
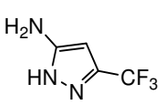
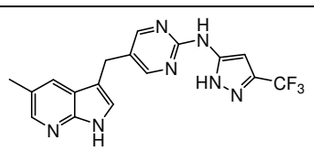
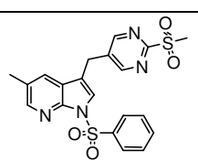
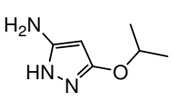
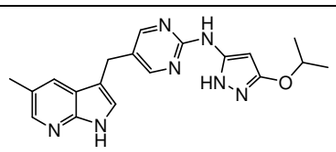
pirrolo[2,3-b]piridina (columna 2) y aminUn compuesA (columna 3) used en el Paso 1 a afford te desired compuesA (columna 4). El compuesto number es provided in columna 1, y elobserved mass es in columna 5.

Tabla 4

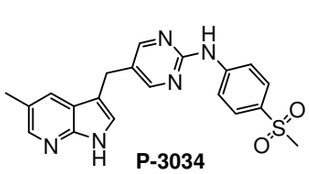
# de compuesto	pirrolo[2,3-b]piridina	Estructura Amino	Estructura del compuesto	MS (ESI) $[M+H^+]^+$
P-3051				328.0
P-3052				377.9
P-3005				300.0
P-3006				356.3
P-3007				314.2
P-3010				334.1

P-3059				370.8
P-3060				354.0
P-3014				353.9
P-3063				369.9
P-3064				365.9
P-3017				353.9
P-3018				384.9
P-3020				347.1
P-3021				346.2

P-3022				363.9
P-3023				363.9
P-3024				374.0
P-3025				344.0
P-3026				360.0
P-3027				501.3
P-3028				399.9
P-3029				362.0
P-3030				372.0

P-3031				482.3
P-3032				346.0
P-3033				362.1
P-3035				334.2
P-3036				333.9
P-3037				374.0
P-3038				363.9

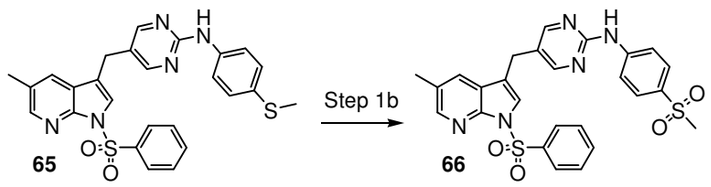
[0677] (4-Metanosulfonil-fenil)-[5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidin-2-il]-amino **P-3034**



P-3034

se prepara al oxidizar el producto del Esquema 9 Paso 1a en la Preparación de[5-(5-

metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidin-2-il]-(4-metilsulfanil-fenil)-amino (**P-3033**), antes de la reacción del Paso 2, de acuerdo con los siguientes Paso 1b:



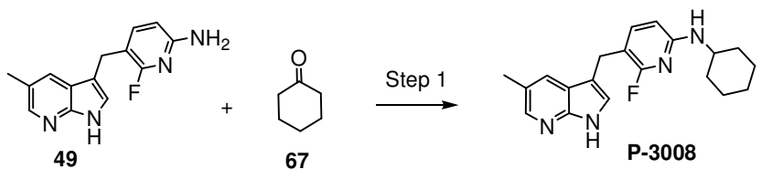
*Paso 1b – Preparación de[5-(1-bencenosulfonil-5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidin-2-il]-(4-metanosulfonil-fenil)-amino (**66**):*

[0678] **A** [5-(1-bencenosulfonil-5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidin-2-il]-(4-metilsulfanil-fenil)-amino (**65**, 80 mg, 0.16 mmol) en 10.0 mL de diclorometano, se añade ácido meta-clorperoxibenzóico (78.6 mg, 0.351 mmol) a 0 ^{o}C. La reacción se agita a temperatura ambiente por 30 minutos, luego se concentra bajo vacío para proporcionar [5-(1-bencenosulfonil-5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-pirimidin-2-il]-(4-metanosulfonil-fenil)-amino **66**, la cual se hace reacciónar de acuerdo con el Esquema 9 Paso 2 para proporcionar el compuesto deseado(**P-3034**, 30.7 mg). MS (ESI) $[M+H^{+}]^{+}$ = 393.9.

Ejemplo 10: Síntesis de ciclohexil-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amino P-3008.

[0679] Ciclohexil-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amino **P-3008** se prepara en 1 Paso a partir de 6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-ilamina **49** y ciclohexanona **67** como se muestra en el Esquema 10.

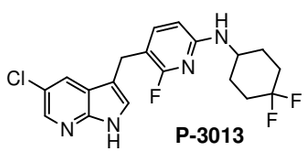
Esquema 10



*Paso 1 – Preparación deciclohexil-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amino (**P-3008**):*

[0680] A 6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-ilamina (**49**, 100 mg, 0.39 mmol) y ciclohexanona (**67**, 0.0465 mL, 0.449 mmol) en 3.00 mL de acetonitrilo, se añade trietilsilano (0.400 mL, 2.50 mmol) y ácido trifluoroacético (0.300 mL, 3.89 mmol). La reacción se agita a 80 ^{o}C toda la noche, luego se extrae con acetato de etilo y 1N bicarbonato de sodio acuoso. La capa orgánica se lava con 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 de gel de silicio, eluyendo con 0-60% acetato de etilo en hexano. Las fracciones apropiadas se combinaros y concentraron bajo vacío para proporcionar el compuesto deseado(**P-3008**, 115 mg). MS (ESI) $[M+H^+]^+$ = 339.0.

[0681] [5-(5-Cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-6-fluoro-piridina-2-il]-(4,4-difluoro-ciclohexil)-amino **P-3013**

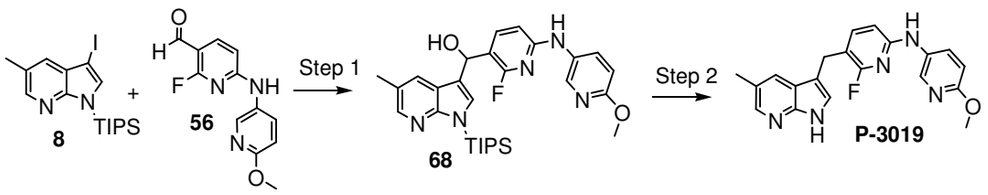


se prepara siguiendo el protocolo del Esquema 10, reemplazando 6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-ilamina **49** con 5-(5-cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-6-fluoro-piridina-2-ilamina **50** y reemplazando ciclohexanona **67** con 4,4-difluoro-ciclohexanona. MS (ESI) $[M+H^+]^+$ = 394.9 y 396.9.

Ejemplo 11: Síntesis de [6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amino P-3019.

[0682] [6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amino **P-3019** se prepara en dos Pasos a partir de 3-yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **8** y 2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-carbaldehído**56** como se muestra en el Esquema 11.

Esquema 11



*Paso 6 – Preparación de[2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-(5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina-3-il)-metanol (**68**):*

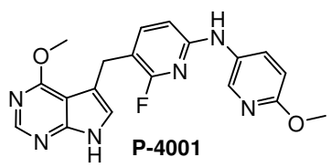
[0683] A una solución de 3-yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**8**, 1.02 g, 2.461 mmol) en 6.0 mL de tetrahidrofurano a -50 ^{o}C bajo nitrógeno, se añaden lentamente cloruro de isopropilmagnesio (1.23 mL, 2.00 M en tetrahidrofurano, 2.46 mmol). La reacción se deja calentar a 5 ^{o}C por 70 minutos, luego se enfría a -45 ^{o}C, seguida por la adición de 2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-carbaldehído(**56**, 0.165 g, 0.667 mmol) en 2.0 mL de tetrahidrofurano. La reacción se deja calentar a temperatura ambiente por 1 hora, luego se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y

concentran bajo vacío para proporcionar el compuesto deseado(**68**, 330 mg). MS (ESI) $[M+H^+]^+$ = 536.2.

*Paso 7 – Preparación de[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amino (**P-3019**):*

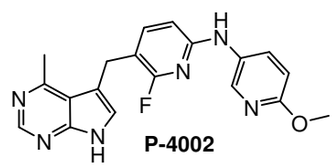
[0684] A [2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-(5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina-3-il)-metanol (**68**, 0.220 g, 0.411 mmol) en 20.0 mL de 1,2-dicloroetano, se añaden trietilsilano (2.0 mL, 12 mmol) y ácido trifluoroacético (1.0 mL, 13 mmol) y la reacción se agita a 80 ^oC por 3 horas. La reacción se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**P-3019**, 105.1 mg). MS (ESI) $[M+H^+]^+$ = 364.2.

[0685] [6-Fluoro-5-(4-metoxi-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amino **P-4001** y [6-Fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amino **P-4002**



P-4001

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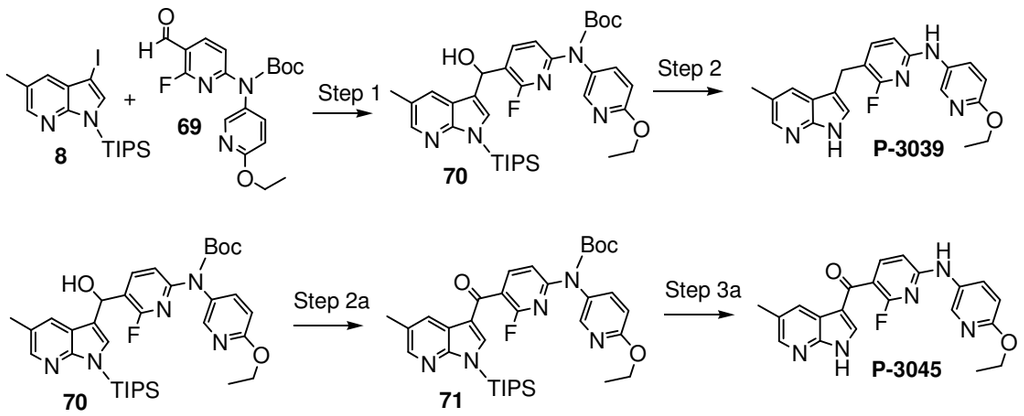
P-4002

se preparan de forma similar al protocolo del Esquema 11, reemplazando 3-yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **8** con 5-yodo-4-metoxi-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina **14** y 5-yodo-4-metil-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina **16**, respectivamente en el Paso 1.

Ejemplo 12: Síntesis de (6-etoxi-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amino P-3039 o [6-(6-etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrolo[2,3-b]piridina-3-il)-metanona P-3045.

[0686] (6-Etoxi-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amino **P-3039** o [6-(6-etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrolo[2,3-b]piridina-3-il)-metanona **P-3045** se preparan en dos Pasos o tres Pasos a partir de 3-yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **8**, y (6-etoxi-piridina-3-il)-(6-fluoro-5-formil-piridina-2-il)-éter terbutílico de ácido carbámico **69** como se muestra en el Esquema 12.

Esquema 12



*Paso 1 – Preparación de (6-Etoxi-piridina-3-il)-{6-fluoro-5-[hidroxi-(5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina-3-il)-metil]-piridina-2-il}-éter terbutílico de ácido carbámico (**70**):*

[0687] A una solución de 3-yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**8**, 0.43 g, 1.0 mmol) en 5 mL de tetrahidrofurano a -40 ^{o}C bajo nitrógeno, se añade lentamente cloruro de isopropilmagnesio (0.51 mL, 2.00 M en tetrahidrofurano, 1.0 mmol). La reacción se deja calentar a -5 ^{o}C por 60 minutos,

luego se enfría a -45 ^{o}C, seguida por la adición de (6-etoxi-piridina-3-il)-(6-fluoro-5-formil-piridina-2-il)-éter terbutílico de ácido carbámico (**69**, 0.06 g, 0.2 mmol) en 2.0 mL de tetrahidrofurano. La reacción se deja calentar a temperatura ambiente por 2 horas, luego se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**70**, 108.1 mg).

*Paso 2 – Preparación de(6-etoxi-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amino (**P-3039**):*

[0688] A (6-etoxi-piridina-3-il)-{6-fluoro-5-[hidroxi-(5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina-3-il)-metil]-piridina-2-il}-éter terbutílico de ácido carbámico (**70**, 108.1 mg, 0.166 mmol) en 4.54 mL de 1,2-dicloroetano, se añaden trietilsilano (0.454 mL, 2.84 mmol) y ácido trifluoroacético (0.27 mL, 3.5 mmol) y la reacción se agita a 80 ^{o}C por 4 horas. La reacción se vierte en carbonato de potasio acuoso y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio eluyendo con 25-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**P-3039**), las cuales se purifican mediante cormatografía adicional.

*Paso 2a – Preparación de(6-etoxi-piridina-3-il)-[6-fluoro-5-(5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina-3-carbonil)-piridina-2-il]-éter terbutílico de ácido carbámico (**71**):*

[0689] (6-Etoxi-piridina-3-il)-{6-fluoro-5-[hidroxi-(5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina-3-il)-metil]-piridina-2-il}-éter terbutílico de ácido carbámico (**70**, 0.400 g, 0.616 mmol) se disuelve alternativamente en 11.8 mL de diclorometano, y se añade Dess-Martin periodinano (0.100 g, 0.236 mmol). La reacción se agita a temperatura ambiente por 30 minutos, luego se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y se concentran bajo vacío para proporcionar el compuesto deseado(**71**, 0.200 g).

*Paso 3a – Preparación de[6-(6-etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrolo[2,3-b]piridina-3-il)-metanona (**P-3045**):*

[0690] A (6-etoxi-piridina-3-il)-[6-fluoro-5-(5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina-3-carbonil)-piridina-2-il]-éter terbutílico de ácido carbámico (**71**, 0.200 g, 0.309 mmol) en 10 mL de 1,2-dicloroetano, y se añade ácido trifluoroacético (0.80 mL, 10.0 mmol). La reacción se agita a 80 ^{o}C por 2 horas, luego se vierte en carbonato de potasio acuoso y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 2-15% metanol in diclorometano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**P-3045**, 60.7 mg). MS (ESI) $[M+H^{+}]^{+}$ = 391.9.

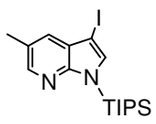
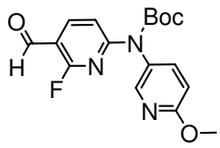
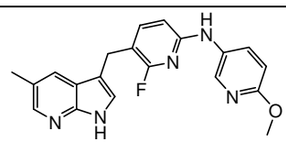
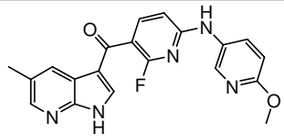
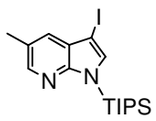
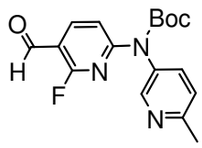
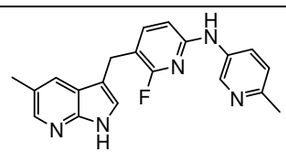
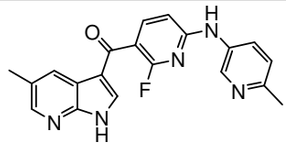
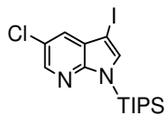
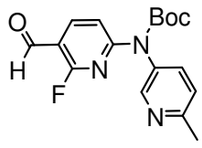
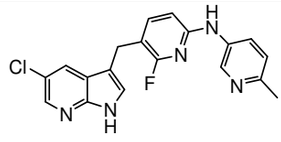
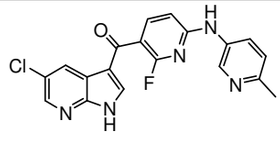
[0691] Los compuestos adicionales se preparan siguiendo el protocolo del Esquema 12. Los compuesto se realizan al sustituir ya sea el 3-yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **8** con 1H-pirrolo[2,3-b]piridina TIPS-progetido apropiado o 7H-pirrolo[2,3-d]pirimidina y (6-etoxi-piridina-3-il)-(6-fluoro-5-formil-piridina-2-il)-éter terbutílico de ácido carbámico **69** con a aldehído Boc-protegido apropiado en el Paso 1. Los siguientes compuestos se realizan usando este procedimiento:
[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-il]-(6-metoxi-piridina-3-il)-amino (**P-3019**),
[2-Fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-(5-metil-1H-pirrolo[2,3-b]piridina-3-il)-metanona(**P-3040**),
[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-il]-(6-metil-piridina-3-il)-amino (**P-3041**),
[5-(5-Cloro-1H-pirrolo[2,3-b]piridina-3-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amino (**P-3042**),
[2-Fluoro-6-(6-metil-piridina-3-ilamino)-piridina-3-il]-(5-metil-1H-pirrolo[2,3-b]piridina-3-il)-metanona (**P-3043**),
(5-Cloro-1H-pirrolo[2,3-b]piridina-3-il)-[2-fluoro-6-(6-metil-piridina-3-ilamino)-piridina-3-il]-metanona(**P-3044**),
(6-Etil-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amino (**P-3048**),
[6-(6-Etil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrolo[2,3-b]piridina-3-il)-metanona(**P-3049**),
(6-Cloro-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amino (**P-4051**),

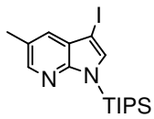
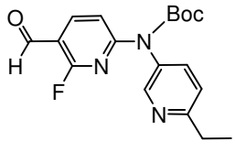
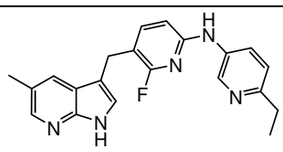
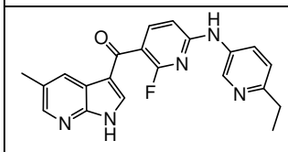
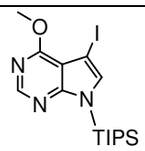
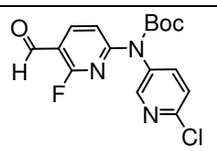
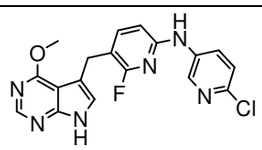
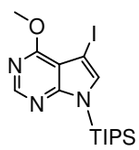
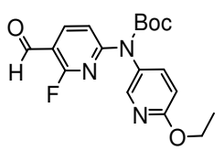
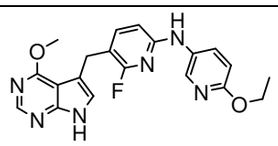
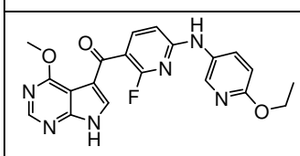
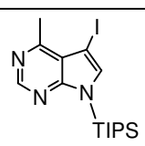
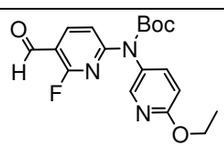
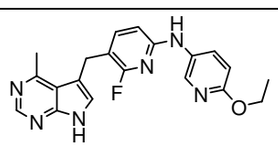
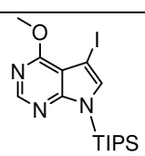
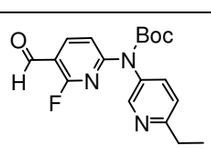
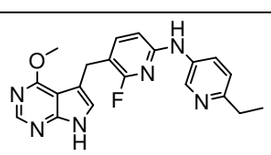
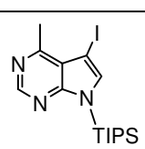
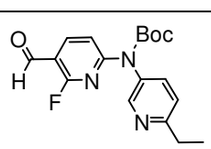
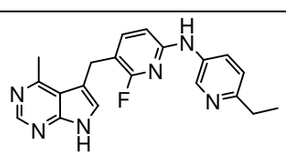
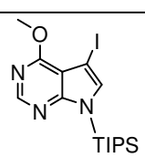
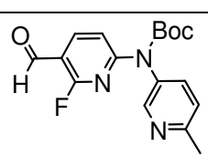
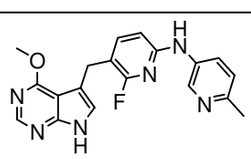
(6-Etoxi-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amino (**P-4005**), (6-Etoxi-piridina-3-il)-[6-fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amino (**P-4006**), (6-Etil-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amino (**P-4007**), (6-Etil-piridina-3-il)-[6-fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amino (**P-4009**), [6-Fluoro-5-(4-metoxi-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-(6-metil-piridina-3-il)-amino (**P-4010**), (1-Etil-1H-pirazol-4-il)-[6-fluoro-5-(4-metoxi-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amino (**P-4059**), [5-(4-Etoxi-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(1-etil-1H-pirazol-4-il)-amino (**P-4060**), (1-Etil-1H-pirazol-4-il)-[6-fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amino (**P-4061**), [5-(4-Etoxi-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amino (**P-4017**), [5-(4-Etoxi-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-amino (**P-4018**), (6-Bromo-piridina-3-il)-[5-(4-etoxi-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-amino (**P-4020**),

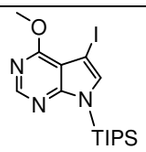
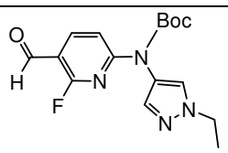
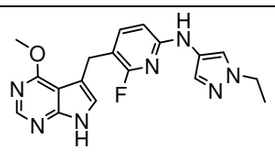
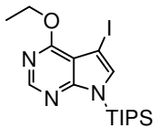
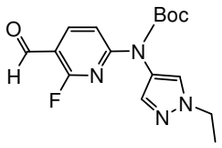
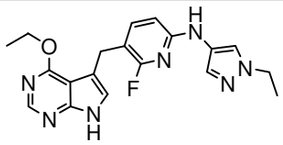
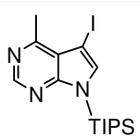
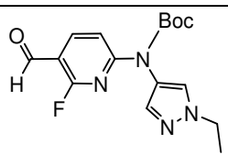
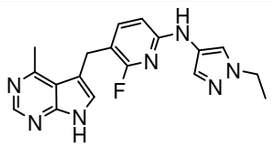
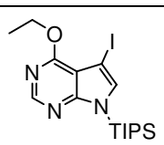
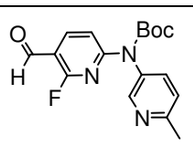
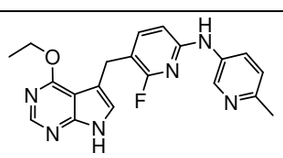
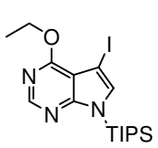
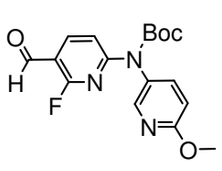
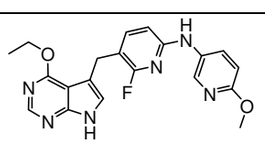
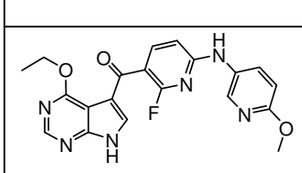
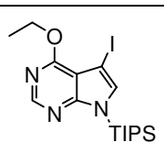
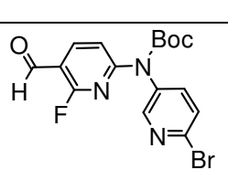
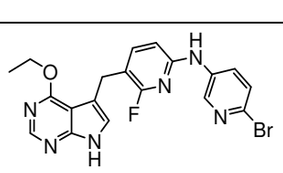
Los siguientesTabla indicatos te TIPS-protected 1H-pirrolo[2,3-b]piridina (columna 2) y Boc-protected Aldehído compuesA (columna 3) used en el Paso 1 a afford te

desired compuesA (columna 4). El compuesto number es provided in columna 1, y elobserved mass es in columna 5.

Tabla 5

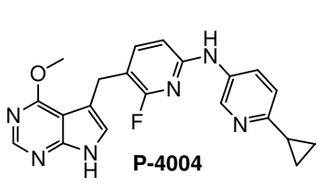
# Compuesto	pirrolo[2,3-b]piridina o pirrolo[2,3-d]pirimidina	Aldehído	Estructura del Compuesto	MS (ESI) $[M+H^+]^+$
P-3019				363.9
P-3040				378.0
P-3041				347.8
P-3043				361.9
P-3042				367.9
P-3044				382.0

P-3048				362.0
P-3049				376.1
P-4051				385.0
P-4005				394.95
P-4024				409.2
P-4006				378.95
P-4007				379.0
P-4009				
P-4010				365.0

P-4059				367.9
P-4060				382.1
P-4061				351.9
P-4017				379.0
P-4018				394.8
P-4025				409.2
P-4020				442.9 444.9

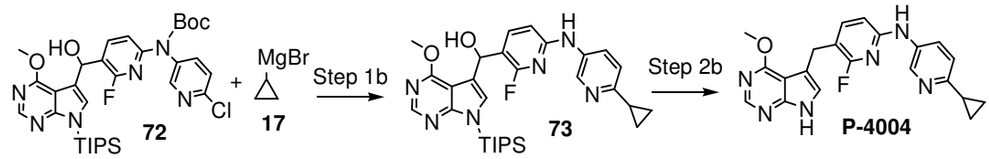
BUSCAR

[0692] (6-Ciclopropil-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amino **P-4052**



P-4004

se prepara a partir del aislado intermedio después del Paso 1 en la Preparación de **P-4051** de acuerdo con los siguientes Pasos 1b y 2b.



*Paso 1b – Preparación de [6-(6-ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-metoxi-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina-5-il)-metanol (**73**):*

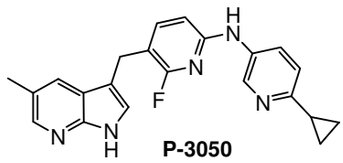
[0693] A (6-cloro-piridina-3-il)-{6-fluoro-5-[hidroxi-(4-metoxi-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina-5-il)-metil]-piridina-2-il}-éter terbutílico de ácido carbámico (**72**, 105 mg, 0.160 mmol) en 3.8 mL del tolueno, se añade complejo [1,1'-bes(diel fenilfosfino)ferroceno] dicloropaladio(II) 1:1 con diclorometano (13.0 mg, 0.064 mmol) es bajo una atmósfera de nitrógeno. La reacción se agita por 5 minutos, luego se añade lentamente bromuro de ciclopropilmagnesio (**17**, 1.60 mL, 1.0 M en tetrahidrofurano, 1.60 mmol). La reacción se calienta a 65 ^{o}C fo 5 horas, luego se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. El material resultante se purifica mediante cromatografía de columna de gel de silicio, eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y se concentran bajo vacío para proporcionar el compuesto deseado (**73**, 70 mg). MS (ESI) $[M+H^+]^+$ = 563.6.

*Paso 2b – Preparación de (6-ciclopropil-piridina-3-il)-[6-fluoro-5-(4-metoxi-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-piridina-2-il]-amino (**P-4052**):*

[0694] A [6-(6-ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-metoxi-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina-5-il)-metanol (**73**, 70 mg, 0.12 mmol) en 10.0 mL del 1,2-dicloroetano, se añaden trietilsilano (1.00 mL, 6.26 mmol) y

ácido trifluoroacético (0.60 mL, 7.8 mmol) y la reacción se agita a 80 ^{o}C por 4 horas. La reacción se vierte en carbonato de potasio acuoso y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. El material resultante se purifica mediante cromatografía de columna de gel de silicio, eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y se concentran bajo vacío para proporcionar el compuesto deseado (**P-4052**, 11.8 mg). MS (ESI) $[M+H^+]^+$ = 390.9.

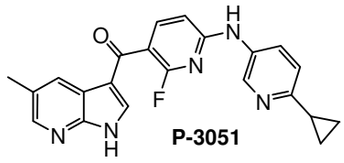
[0695] (6-Ciclopropil-piridina-3-il)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amino **P-3050**



P-3050

se prepara de forma similar al protocolo del Esquema 12, Paso 1, seguido por los Pasos 1b y 2b, donde(6-etoxi-piridina-3-il)-(6-fluoro-5-formil-piridina-2-il)-éter terbutílico de ácido carbámico **69** se reemplaza con (6-cloro-piridina-3-il)-(6-fluoro-5-formil-piridina-2-il)-éter terbutílico de ácido carbámico en el Paso 1. MS (ESI) $[M+H^+]^+$ = 374.2.

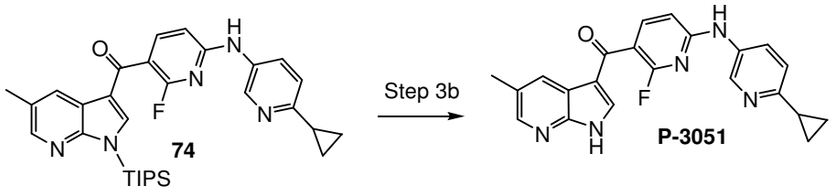
[0696] [6-(6-Ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrolo[2,3-b]piridina-3-il)-metanona**P-3051**



P-3051

se prepara de forma similar a partir del intermedio formado a partir del Paso 1b en la

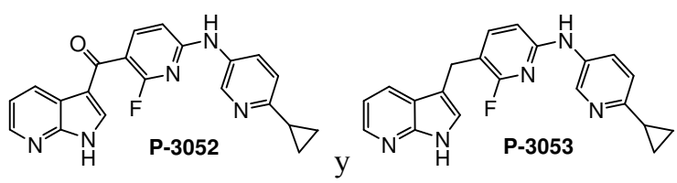
Preparación de **P-3050**, reacciónando de forma similar al Paso 2a del Esquema 12, y luego de acuerdo con el siguiente Paso 3b.



*Paso 3b – Preparación de[6-(6-ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1H-pirrolo[2,3-b]piridina-3-il)-metanona (**P-3051**):*

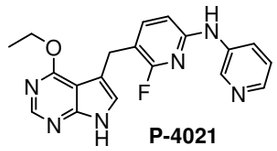
[0697] A [6-(6-ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina-3-il)-metanona (**74**, 134 mg, 0.25 mmol) en 10 mL de tetrahidrofurano, se añaden fluoruro de tetrabutilamonio trihidrato (85.53 mg, 0.27 mmol) y la reacción se agita a temperatura ambiente por 30 minutos. Se añade agua y la mezcla se extrae con acetato de etilo. La capa orgánica se lava con salmuera agua y salmuera, se seca con sulfato de magnesio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**P-3051**, 82 mg). MS (ESI) $[M+H^+]^+ = 388.0$.

[0698] [6-(6-Ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(1H-pirrolo[2,3-b]piridina-3-il)-metanona **P-3052** y (6-Ciclopropil-piridina-3-il)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridina-3-ilmetil)-piridina-2-il]-amino **P-3053**



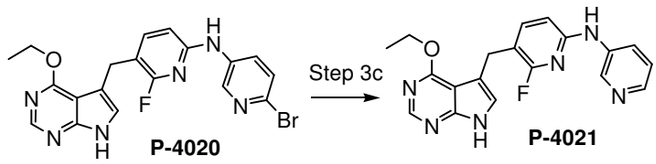
se prepararon de forma similar a los protocolos usados para **P-3051** y **P-3052**, respectivamente, donde 3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (preparados de forma similar al protocolo del Esquema 1, reemplazando 5-cloro-1H-pirrolo[2,3-b]piridina **1** con 1H-pirrolo[2,3-b]piridina en el Paso 1) se uso en lugar de 3-yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **8** en el Paso 1. **P-3052** MS (ESI) $[M+H^+]^+ = 374.0$. **P-3053** MS (ESI) $[M+H^+]^+ = 359.9$.

[0699] [5-(4-Etoxi-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-6-fluoro-piridina-2-il]-piridina-3-il-amino **P-4021**



P-4021

se prepara partir de (6-bromo-piridina-3-il)-[5-(4-etoxi-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-6-fluoro-piridina-2-il]-amino **P-4020** de acuerdo con el siguiente Paso 3c.



P-4020 **P-4021**

*Paso 3b – Preparación de[5-(4-etoxi-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-6-fluoro-piridina-2-il]-piridina-3-il-amino (**P-4021**):*

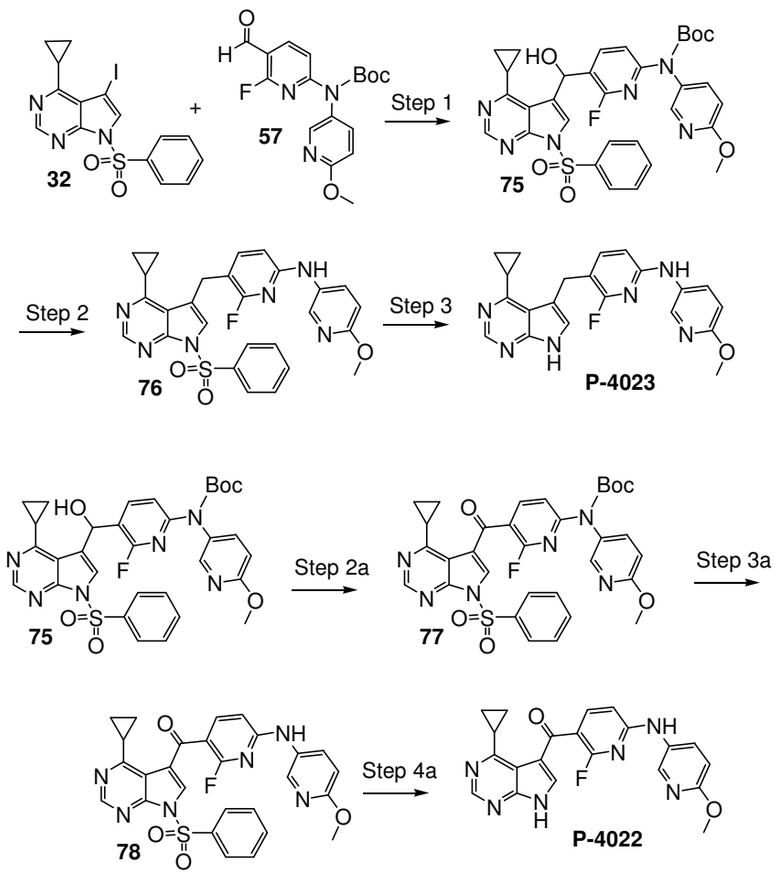
[0700] A (6-bromo-piridina-3-il)-[5-(4-etoxi-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-6-fluoro-piridina-2-il]-amino (**P-4020**, 0.040 g, 0.090 mmol) en 5.0 mL de tetrahidrofurano bajo nitrógeno a -78 ^oC, se añade tert-butillitio (0.531 mL, 1.70 M en hexano, 0.903 mmol). La reacción se agita a -78 ^oC por 30 minutos, luego se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. El material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 20-100%

acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**P-4021**, 25.7 mg). MS (ESI) $[M+H^+]^+$ = 364.9.

Ejemplo 13: Síntesis de [5-(4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-amino P-4023 or (4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-[2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-metanona P-4022.

[0701] [5-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-amino **P-4023** o 4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-[2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-metanona **P-4022** se preparan en tres pasos o cuatro pasos a partir de 7-bencenosulfonil-4-ciclopropil-5-yodo-7H-pirrolo[2,3-d]pirimidina **32** y (6-fluoro-5-formil-piridina-2-il)-(6-metoxi-piridina-3-il)-éter terbutílico de ácido carbámico **57** como se muestra en el Esquema 13.

Esquema 13



*Paso 1 – Preparación de {5-[(7-bencenosulfonil-4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-hidroxi-metil]-6-fluoro-piridina-2-il}-(6-metoxi-piridina-3-il)-éter terbutílico de ácido carbámico (**75**):*

[0702] A una solución de 7-bencenosulfonil-4-ciclopropil-5-yodo-7H-pirrolo[2,3-d]pirimidina (**32**, 0.760 g, 1.79 mmol) en 5.43 mL de tetrahidrofurano at -40 ^{o}C bajo nitrógeno, se añade lentamente cloruro de isopropilmagnesio (0.892 mL, 2.0 M en tetrahidrofurano, 1.78mmol). La reacción se deja calentar a -5 ^{o}C por 75 minutos, luego se enfría a -45 ^{o}C y se añade (6-fluoro-5-formil-piridina-2-il)-(6-metoxi-piridina-3-il)-éter terbutílico de ácido carbámico (**57**, 0.38 g, 1.1 mmol) en 2.0 mL de tetrahidrofurano. La reacción se deja calentar a temperatura ambiente por 2 horas, luego se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en

sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**75**, 0.64 g). MS (ESI) $[M+H^+]^+$ = 647.2.

*Paso 2 – Preparación de[5-(7-Bencenosulfonil-4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-amino (**76**):*

[0703] A {5-[(7-bencenosulfonil-4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-hidroxi-metil]-6-fluoro-piridina-2-il}-(6-metoxi-piridina-3-il)-éter terbutílico de ácido carbámico (**75**, 0.290 g, 0.448 mmol) en 9.93 mL de 1,2-dicloroetano, se añaden trietilsilano (0.31 mL, 2.0 mmol) y ácido trifluoroacético (0.16 mL, 2.0 mmol) y la reacción se agita a 80 ^oC por 4 horas. La reacción se vierte en carbonato de potasio acuoso y se extrae con acetato de etilo. La capa orgánica se seca con sulfato de sodio, se filtra y el filtrado se concentra bajo vacío para proporcionar el compuesto deseado(**76**, 170 mg). MS (ESI) $[M+H^+]^+$ = 530.9.

*Paso 3 – Preparación de[5-(4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-amino (**P-4023**):*

[0704] A [5-(7-bencenosulfonil-4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-amino (**76**, 0.170 g, 0.320 mmol) en 10.0 mL de tetrahidrofurano, se añade fluoruro de tetrabutilamonio, trihidraA (0.174 g, 0.551 mmol) y la reacción se agita a temperatura ambiente toda la noche. La reacción se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca con sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de

silicio, eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**P-4023**, 100.4 mg). MS (ESI) $[M+H^+]^+$ = 390.8.

*Paso 2a – Preparación de[5-(7-bencenosulfonil-4-ciclopropil-7H-pirrolo[2,3-d]pirimidina-5-carbonil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-éter terbutílico de ácido carbámico (**77**):*

[0705] {5-[(7-Bencenosulfonil-4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-hidroxi-metil]-6-fluoro-piridina-2-il}-(6-metoxi-piridina-3-il)-éter terbutílico de ácido carbámico (**75**, 0.350 g, 0.541 mmol) se disuelve alternativamente en 10.0 mL de diclorometano, y se añade Dess-Martin periodinano (0.211 g, 0.498 mmol). La reacción se agita a temperatura ambiente por 30 minutos, luego se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 10-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y se concentran bajo vacío para proporcionar el compuesto deseado(**77**, 340 mg). MS (ESI) $[M+H^+]^+$ = 645.4.

*Paso 3a – Preparación de(7-bencenosulfonil-4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-[2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-metanona (**78**):*

[0706] A [5-(7-bencenosulfonil-4-ciclopropil-7H-pirrolo[2,3-d]pirimidina-5-carbonil)-6-fluoro-piridina-2-il]-(6-metoxi-piridina-3-il)-éter terbutílico de ácido carbámico (**77**, 0.340 g, 0.527 mmol) en 10 mL de 1,2-dicloroetano, se añade ácido trifluoroacético (0.80 mL, 10.4 mmol). La reacción se agita a 80 ^oC por 45 minutos, luego se vierte en carbonato de potasio acuoso y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo

vacío para proporcionar el compuesto deseado(**78**, 235 mg). MS (ESI) $[M+H^+]^+$ = 545.4.

*Paso 4a – Preparación de(4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-[2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-metanona (**P-4022**):*

[0707] A (7-bencenosulfonil-4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-[2-fluoro-6-(6-metoxi-piridina-3-ilamino)-piridina-3-il]-metanona (**78**, 0.235 g, 0.432 mmol) en 10.0 mL de tetrahidrofurano, se añade fluoruro de tetrabutilamonio trihidrato(0.174 g, 0.551 mmol). La reacción se agita a temperatura ambiente toda la noche, luego se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y se concentranbajo vacío para proporcionar el compuesto deseado(**P-4022**, 104.5 mg). MS (ESI) $[M+H^+]^+$ = 405.0.

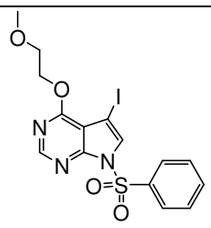
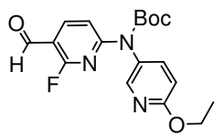
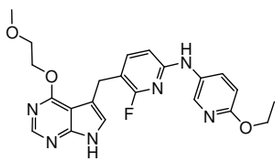
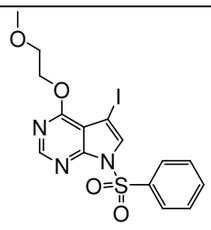
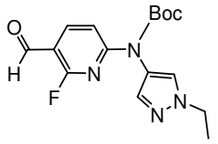
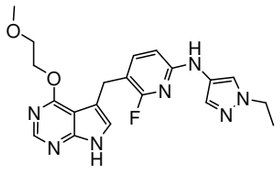
[0708] Los compuestos se preparan siguiendo el protocolo del Esquema 13. Puede usarse 4-Ciclopropil-5-yodo-7-(tolueno-4-sulfonil)-7H-pirrolo[2,3-d]pirimidina **33** en lugar de 7-bencenosulfonil-4-ciclopropil-5-yodo-7H-pirrolo[2,3-d]pirimidina **32**. Los compuestos se realizan al sustituir 7-bencenosulfonil-4-ciclopropil-5-yodo-7H-pirrolo[2,3-d]pirimidina **32** con a bencenosulfonil apropiado o 4-metibencenosulfonil-protegido 7H-pirrolo[2,3-d]pirimidina o 1H-pirrolo[2,3-b]piridina y (6-etoxi-piridina-3-il)-(6-fluoro-5-formil-piridina-2-il)-éter terbutílico de ácido carbámico **57** con a aldehído Boc-protegido apropiado en el Paso 1. En algunos casos, se usa un aldehído no Boc protegido como se indica en la siguiente tabla (sin el Paso 3a en este caso). Los siguientes compuestos se realizan usando

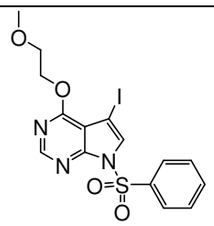
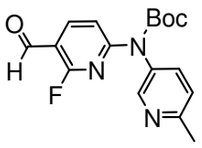
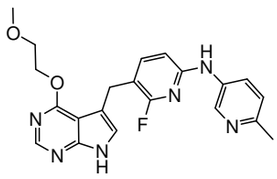
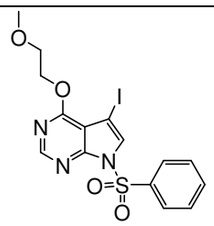
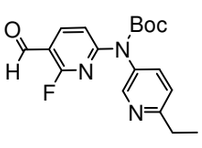
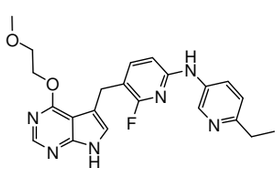
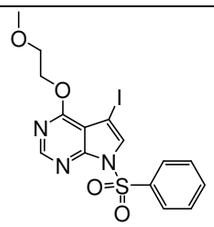
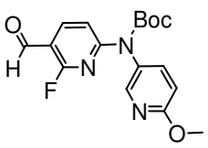
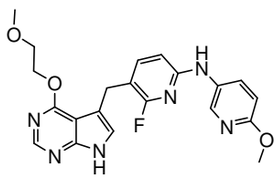
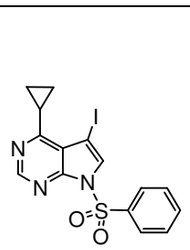
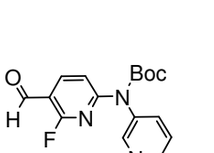
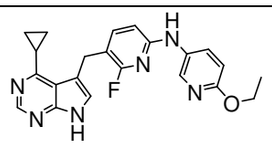
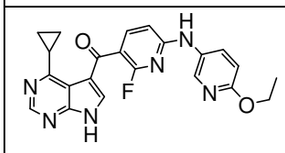
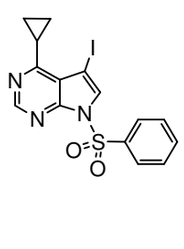
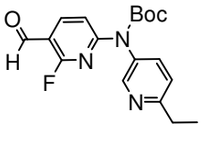
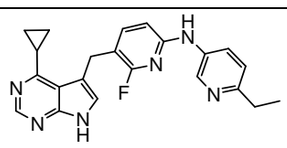
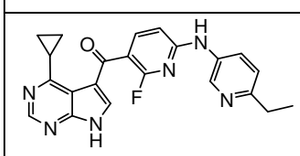
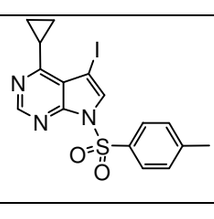
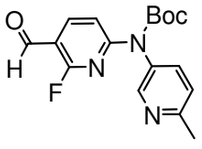
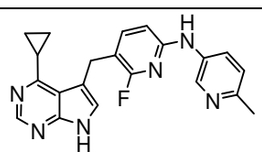
este procedimiento: (6-Etoxi-piridina-3-il)-{6-fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrolo[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-amino (**P-4008**), (1-Etil-1H-pirazol-4-il)-{6-fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrolo[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-amino (**P-4014**), {6-Fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrolo[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-(6-metil-piridina-3-il)-amino (**P-4063**), (6-Etil-piridina-3-il)-{6-fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrolo[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-amino (**P-4064**), {6-Fluoro-5-[4-(2-metoxi-etoxi)-7H-pirrolo[2,3-d]pirimidina-5-ilmetil]-piridina-2-il}-(6-metoxi-piridina-3-il)-amino (**P-4019**), [5-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-etoxi-piridina-3-il)-amino (**P-4026**), (4-Ciclopropil-7H-pirrolo[2,3-d]pirimidina-5-il)-[6-(6-etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-metanona(**P-4027**), [5-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-etil-piridina-3-il)-amino (**P-4028**), (4-Ciclopropil-7H-pirrolo[2,3-d]pirimidina-5-il)-[6-(6-etil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-metanona(**P-4029**), [5-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(6-metil-piridina-3-il)-amino (**P-4030**), (4-Ciclopropil-7H-pirrolo[2,3-d]pirimidina-5-il)-[2-fluoro-6-(6-metil-piridina-3-ilamino)-piridina-3-il]-metanona(**P-4031**), [6-(6-Etoxi-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-metil-7H-pirrolo[2,3-d]pirimidina-5-il)-metanona(**P-4032**),

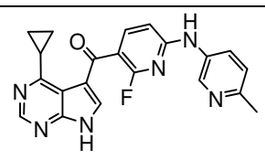
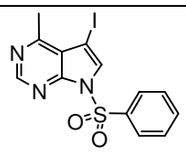
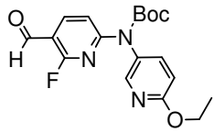
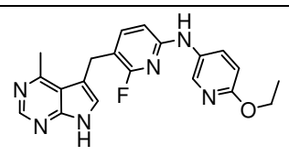
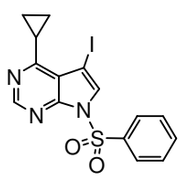
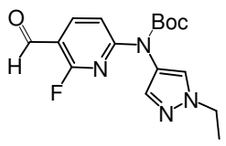
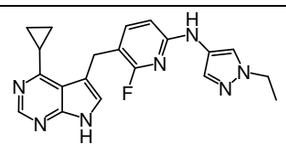
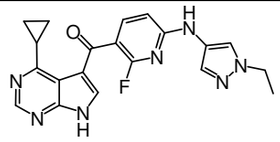
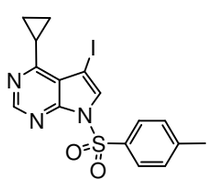
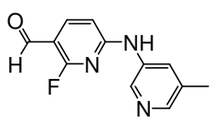
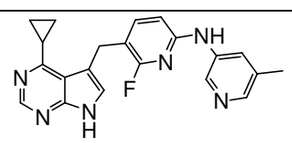
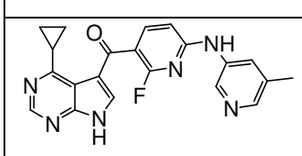
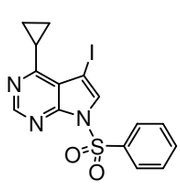
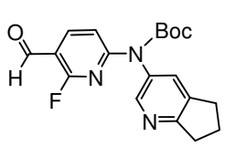
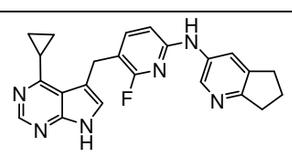
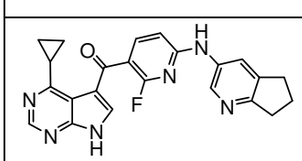
[5-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(1-etil-1H-pirazol-4-il)-amino (**P-4036**), (4-Ciclopropil-7H-pirrolo[2,3-d]pirimidina-5-il)-[6-(1-etil-1H-pirazol-4-ilamino)-2-fluoro-piridina-3-il]-metanona(**P-4037**), [5-(4-Ciclopropil-7H-pirrolo[2,3-d]pirimidina-5-ilmetil)-6-fluoro-piridina-2-il]-(5-metil-piridina-3-il)-amino (**P-4038**), (4-Ciclopropil-7H-pirrolo[2,3-d]pirimidina-5-il)-[2-fluoro-6-(5-metil-piridina-3-ilamino)-piridina-3-il]-metanona(**P-4039**),

La siguiente Tabla indica el 1H-pirrolo[2,3-b]piridina Bencenosulfonil-protegido (columna 2) y el compuesto Aldehído Boc-protegido (columna 3) usado en el Paso 1 para lograr el compuesto deseado (columna 4). El número del compuesto se muestra en la columna 1, y la masa observada en la columna 5.

Tabla 6

# Compuesto	pirrolo[2,3-b]piridina	Aldehído	Estructura del Compuesto	MS (ESI) $[M+H^+]^+$
P-4008				439.0
P-4014				412.0

P-4063				409.0
P-4064				423.0
P-4019				424.9
P-4026				404.9
P-4027				418.8
P-4028				389.0
P-4029				402.9
P-4030				375.0

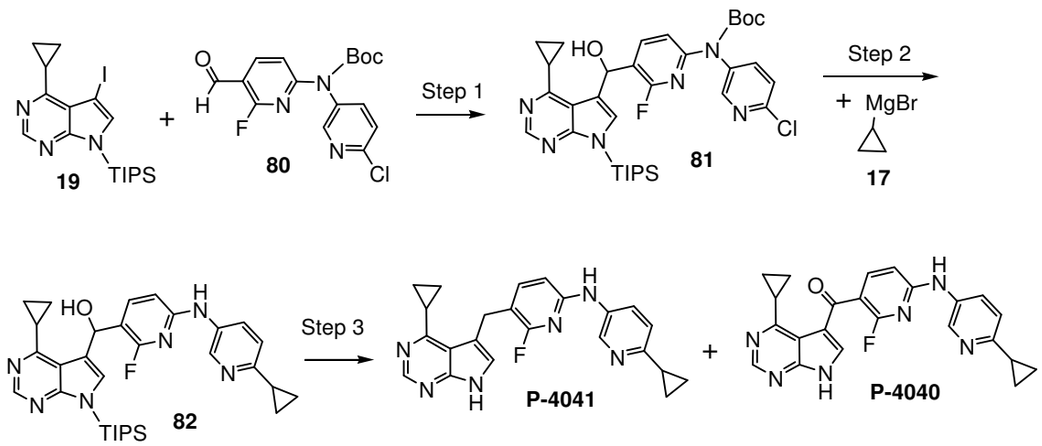
P-4031				388.9
P-4032				393.1
P-4036				378.0
P-4037				392.0
P-4038				375.1
P-4039				389.1
P-4042				
P-4043				

Ejemplo 14: Síntesis de [6-(6-ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona P-4040 y (6-

ciclopropil-piridina-3-il)-[5-(4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-6-fluoro-piridina-2-il]-amino P-4041.

[0709] [6-(6-Ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona **P-4040** y (6-ciclopropil-piridina-3-il)-[5-(4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-6-fluoro-piridina-2-il]-amino **P-4041** se preparan en tres Pasos a partir de 4-ciclopropil-5-yodo-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina **19** y (6-cloro-piridina-3-il)-(6-fluoro-5-formil-piridina-2-il)-éter terbutílico de ácido carbámico **80** como se muestra en el Esquema 14.

Esquema 14



*Paso 1 – Preparación de(6-cloro-piridina-3-il)-{5-[(4-ciclopropil-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidin-5-il)-hidroxi-metil]-6-fluoro-piridina-2-il}-éter terbutílico de ácido carbámico (**81**):*

[0710] A 4-ciclopropil-5-yodo-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina (**19**, 0.72 g, 1.64 mmol) en 6.0 mL de tetrahidrofurano a -40 ^{o}C bajo nitrógeno, se añade lentamente cloruro de isopropilmagnesio (0.82 mL, 2.01 M en tetrahidrofurano, 1.65 mmol). La reacción se deja calentar a -5 ^{o}C por 75 minutos, luego se enfría a -45 ^{o}C y se añade (6-cloro-piridina-3-il)-(6-fluoro-5-formil-

piridina-2-il)-éter terbutílico de ácido carbámico (**80**, 0.48 g, 1.38 mmol) en 5.0 mL. La reacción se deja calentar a temperatura ambiente in 2 horas, luego se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**81**, 0.51 g). MS (ESI) $[M+H^+]^+$ = 667.2).

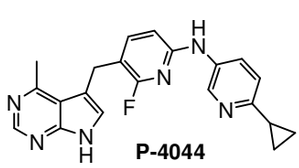
*Paso 2 – Preparación de[6-(6-ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-ciclopropil-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanol (**82**):*

[0711] A (6-cloro-piridina-3-il)-{5-[(4-ciclopropil-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidin-5-il)-hidroxi-metil]-6-fluoro-piridina-2-il}-éter terbutílico de ácido carbámico (**81**, 0.51 g, 0.77 mmol) en 12 mL de tolueno, se añade [1,1'-bis(difenilfosfino) ferroceno]dicloropaladio(II) (0.13 g, 0.17 mmol) bajo nitrógeno y la reacción se agita por 5 minutos. Se añade lentamente bromuro de Ciclopropilmagnesio (**17**, 15.29 mL, 0.50 M en tetrahidrofurano, 7.65 mmol) y la reacción is se calienta a 65 ^oC por 2 horas. La reacción se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 20-100% acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado(**82**, 400 mg).

*Paso 3 – Preparación de[6-(6-ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (**P-4040**) y (6-ciclopropil-piridina-3-il)-[5-(4-ciclopropil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-6-fluoro-piridina-2-il]-amino (**P-4041**):*

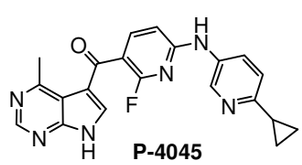
[0712] A [6-(6-ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-ciclopropil-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanol (**82**, 400 mg, 0.7 mmol) en 30 mL de diclorometano, se añaden trietilsilano (2.6 mL, 16.28 mmol) y ácido trifluoroacético (1.5 mL, 15.13 mmol), y la reacción se agita a 80 ^{o}C por 3 horas. La reacción se vierte encarbonato de potasio acuoso y se extrae con acetato de etilo. La capa orgánica se lava con salmuera, se secan en sulfato de sodio, se filtra y el filtrado se concentra bajo vacío. Luego, el material resultante se purifica por cromatografía de columna de gel de silicio, eluyendo con 20-100% acetato de etilo en hexano para dar una mezcla de compuestos **P-4040** y **P-4041**. Éstos se separan mediante HPLC preprativa para proporcionar los compuestos aislados (**P-4040**, 3.0 mg, MS (ESI) $[M+H^+]^+$ = 414.9), (**P-4041**, 37.9 mg, MS (ESI) $[M+H^+]^+$ = 401.0).

[0713] (6-Ciclopropil-piridina-3-il)-[6-fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridina-2-il]-amino **P-4044** y [6-(6-ciclopropil-piridina-3-ilamino)-2-fluoro-piridina-3-il]-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona **P-4045**



P-4044

y



P-4045

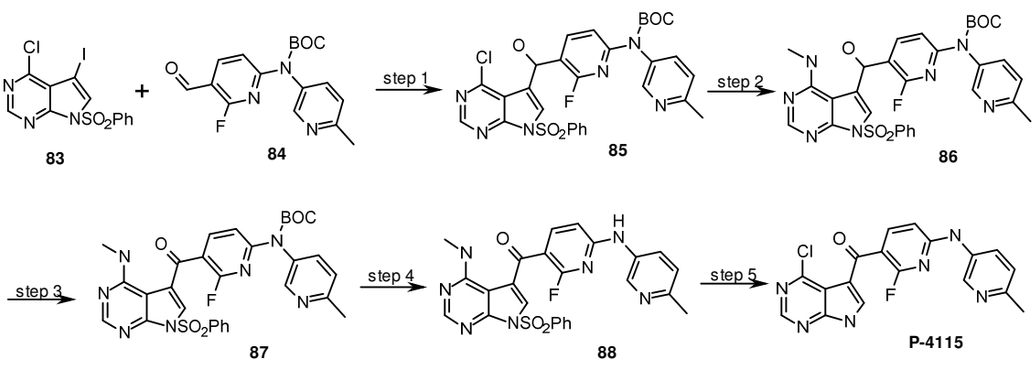
,

se preparan de forma similar al Esquema 14 Esquema 14, donde 4-ciclopropil-5-yodo-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina **19**, se reemplaza en el Paso 1

con 5-yodo-4-metil-7H-pirrolo[2,3-d]pirimidina (preparado de forma similar al Esquema 4 Pasos 1 y 2). **P-4044**, 2.5 mg, MS (ESI) $[M+H^+]^+$ 375.0. **P-4045**, 5.3 mg, MS (ESI) $[M+H^+]^+$ = 388.9.

Ejemplo 15: Síntesis de [2-fluoro-6-[(6-metil-3-piridil)amino]-3-piridil]-[4-(metilamino)-7H-pirrolo[2,3-d]pirimidin-5-il]metanona (P-4115)

Esquema 15



Paso 1- Preparación de tert-butil N-[5-[[7-(bencenosulfonil)-4-cloro-pirrolo[2,3-d]pirimidin-5-il]-hidroxi-metil]-6-fluoro-2-piridil]-N-(6-metil-3-piridil)carbamato

85

[0714] A una solución de 7-(bencenosulfonil)-4-cloro-5-yodo-pirrolo[2,3-d]pirimidina (**1**, 0.43 g, 1.01 mmol) en tetrahidrofurano (5 mL) at -30 °C bajo nitrógeno se añadió lentamente 2.0 M Cloruro de isopropilmagnesio en tetrahidrofurano (0.5 ml). La reacción se deja calentar -5 °C por 75 minutos. Luego, la reacción se enfría a -45 °C, seguido por la adición de tert-butil N-(6-fluoro-5-formil-2-piridil)-N-(6-metil-3-piridil)carbamato (**84**, 0.24 g, 0.72 mmol) en TF (3.0 mL). La reacción se deja calentar a temperatura ambiente por aproximadamente 2 horas. La reacción se vierte en agua, se extrae con acetato de etilo. La capa orgánica se seca en sulfato de sodio anhídro, y se filtra. El filtrado fue concentrado,

purificado con cromatografía de columna de gel de silicio eluyendo con 20%-100% acetato de etilo en hexano para dar el producto (85, 0.41 g, 90.6%). MS (ESI) [M+H+]+ = 625.0.

Paso 2- Preparación de tert-butil N-[5-[[7-(bencenosulfonil)-4-metilamino-pirrolo[2,3-d]pirimidin-5-il]-hidroxi-metil]-6-fluoro-2-piridil]-N-(6-metil-3-piridil)carbamato ***86***

[0715] A tert-butil N-[5-[[7-(bencenosulfonil)-4-cloro-pirrolo[2,3-d]pirimidin-5-il]-hidroxi-metil]-6-fluoro-2-piridil]-N-(6-metil-3-piridil)carbamato (**85**, 75 mg, 0.12 mmol) en alcohol isopropílico (0.80 mL) se añade 2M metilamina en TF (0.6 ml). La solución resultante se agita a 40 ºC por 6 horas. La reacción fue concentrada para dar el producto (86, 70 mg, 94.2%). MS (ESI) [M+H+]+ = 620.

Paso 3–Preparación de tert-butil N-[5-[7-(bencenosulfonil)-4-metilamino-pirrolo[2,3-d]pirimidina-5-carbonil]-6-fluoro-2-piridil]-N-(6-metil-3-piridil)carbamato ***87***

[0716] A tert-butil N-[5-[[7-(bencenosulfonil)-4-metilamino-pirrolo[2,3-d]pirimidin-5-il]-hidroxi-metil]-6-fluoro-2-piridil]-N-(6-metil-3-piridil)carbamato (**86**, 0.07 g, 0.11 mmol) en DCM (10 mL) se añade DMP (0.06 g, 0.14 mmol). La reacción se agita a temperatura ambiente por 20 minutos. La reacción se concentró, y purificó con cromatografía de columna de gel de silicio eluyendo con 20% a 100% acetato de etilo en hexano para dar el producto (**87**, 0.065 g, 93.6%).

Paso 4 – Preparación de[7-(bencenosulfonil)-4-metilamino-pirrolo[2,3-d]pirimidin-5-il]-[2-fluoro-6-[(6-metil-3-piridil)amino]-3-piridil]metanona; 2,2,2-ácido trifluoroacético ***88***

[0717] A tert-butil N-[5-[7-(bencenosulfonil)-4-metilamino-pirrolo[2,3-d]pirimidina-5-carbonil]-6-fluoro-2-piridil]-N-(6-metil-3-piridil)carbamato (**87**, 65 mg, 0.11 mmol) en dicloroetano (10 mL) se añade TFA (0.65 ml, 8.75 mmol). La reacción se calienta 80 ºC por 1 hora. La reacción se concentra para dar un producto crudo (CF3COOH salt) de alrededor de (**88**, 0.080 g, 86.4%). MS (ESI) [M+H+]+ = 518. MS es la base libre del producto.

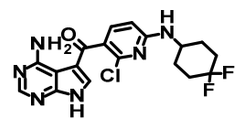
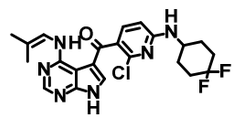
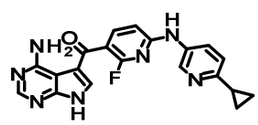
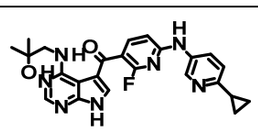
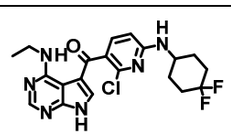
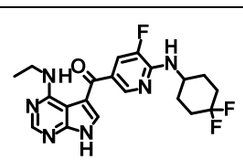
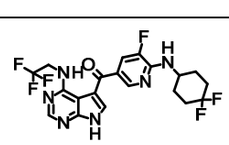
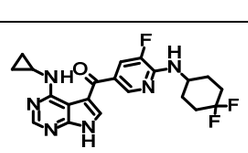
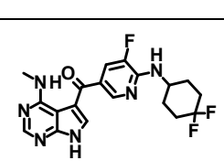
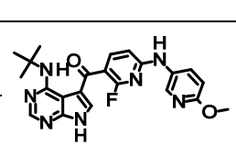
Paso 5 – Preparación de[2-fluoro-6-[(6-metil-3-piridil)amino]-3-piridil]-(4-metilamino-7H-pirrolo[2,3-d]pirimidin-5-il)metanona ***P-4115***

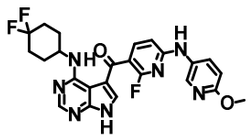
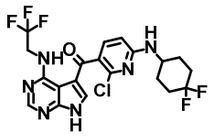
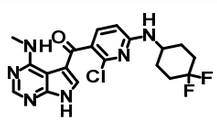
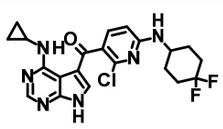
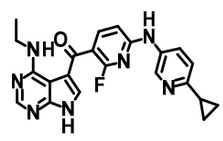
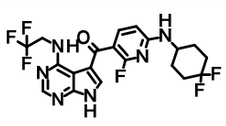
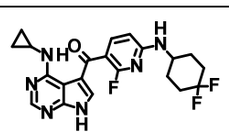
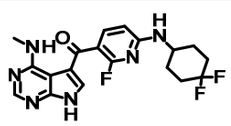
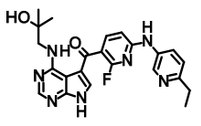
[0718] A [7-(bencenosulfonil)-4-metilamino-pirrolo[2,3-d]pirimidin-5-il]-[2-fluoro-6-[(6-metil-3-piridil)amino]-3-piridil]metanona; se añade 2,2,2-ácido trifluoroacético (**88**, 80 mg, 0.09 mmol) en Metanol (6 ml) y KOH (0.1 g, 1.78 mmol). La reacción se agita a temperatura ambiente por 1 hora. La mezcla de reacción se concentra y purifica mediante cromatografía de columna de gel de silicio eluyendo con 2% a 25% metanol en cloruro de metileno para dar el producto (**P-4115**, 9.6 mg, 27.3%). MS (ESI) [M+H+]+ = 377.9.

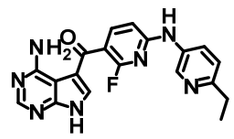
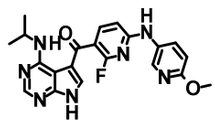
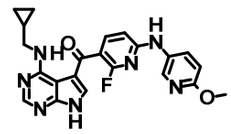
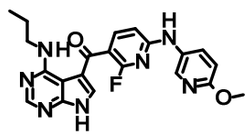
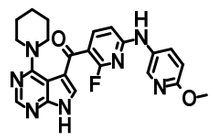
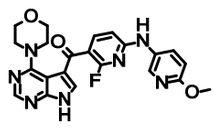
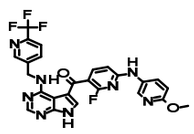
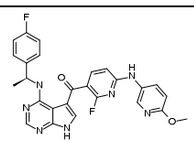
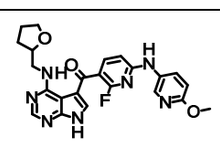
La Tabla 2 describe los compuestos preparados de acuerdo con los protocolos sintéticos establecidos en los Esquemas 14 y 15.

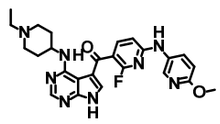
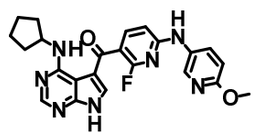
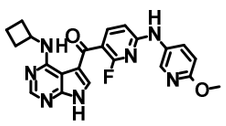
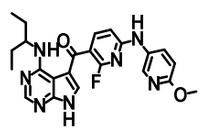
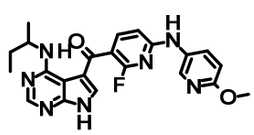
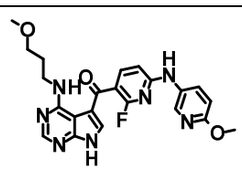
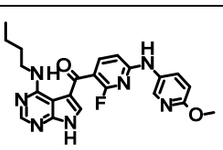
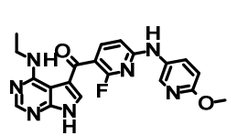
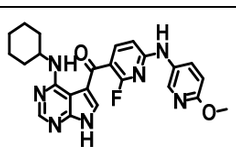
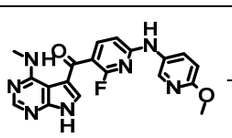
Las estructuras fueron caracterizadas por espectroscopia de masa y espectrocopias RMN de ^{1}H y ^{13}C.

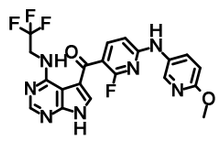
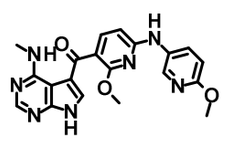
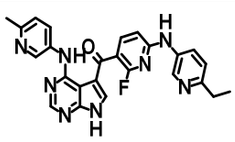
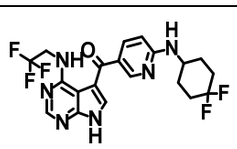
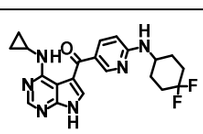
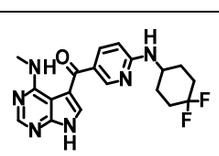
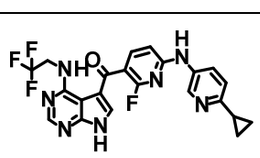
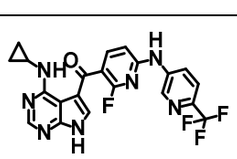
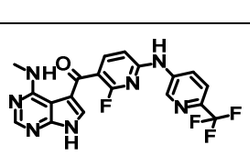
Tabla 2

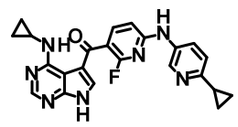
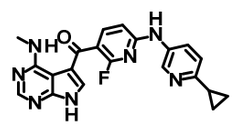
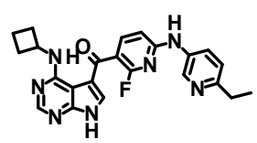
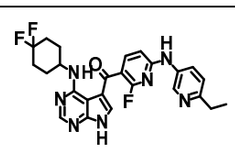
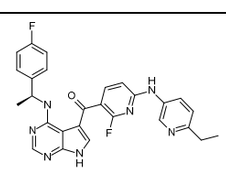
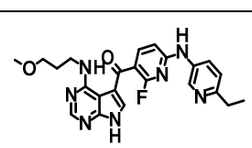
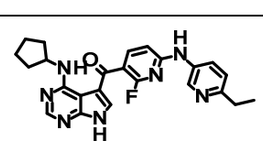
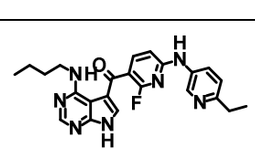
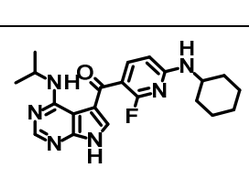
No.	Estructura del Compuesto	MS (ESI) $[M+H^+]^+$
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P-4047		461.3
P-4048		390.1
P-4049		462.1
P-4050		435.0
P-4051		419.0
P-4052		472.95
P-4053		431.0
P-4054		405.0
P-4055		436.5

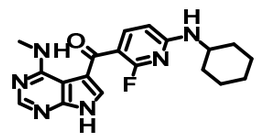
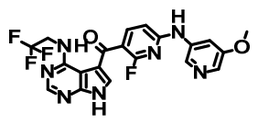
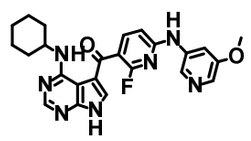
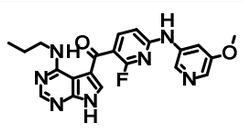
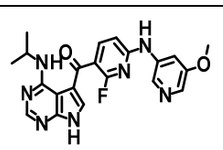
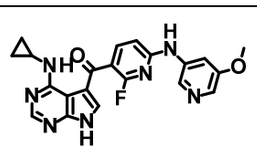
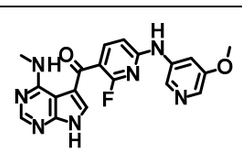
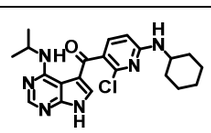
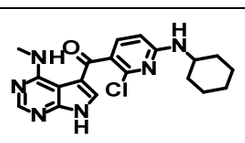
No.	Estructura del Compuesto	MS (ESI) $[M+H^+]^+$
P-4056		498.5
P-4057		489.0
P-4058		420.9
P-4059		447.1
P-4060		418.0
P-4061		473.0
P-4062		431.1
P-4063		405.0
P-4064		445.0

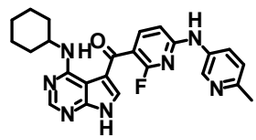
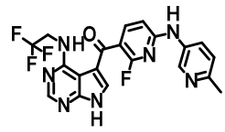
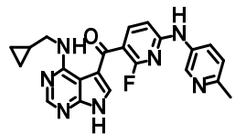
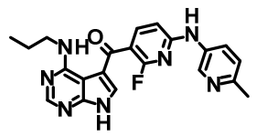
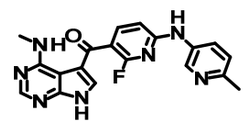
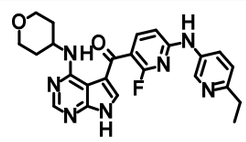
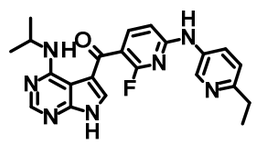
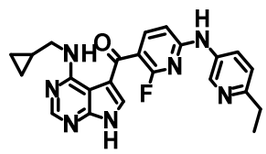
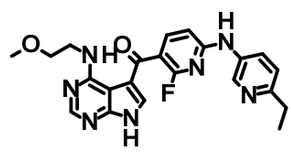
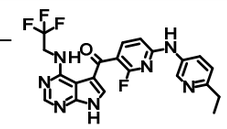
No.	Estructura del Compuesto	MS (ESI) $[M+H^+]^+$
P-4065		377.9
P-4066		422.0
P-4067		434.5
P-4068		422.0
P-4069		449.5
P-4070		450.0
P-4071		539.5
P-4072		502.5
P-4073		464.0

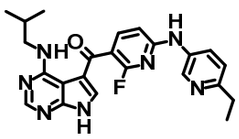
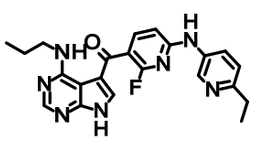
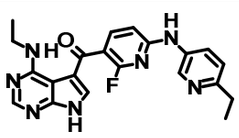
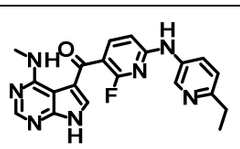
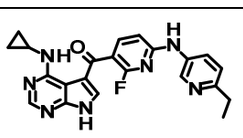
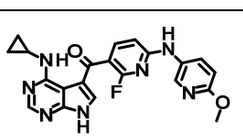
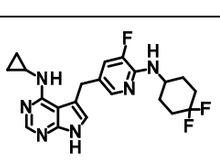
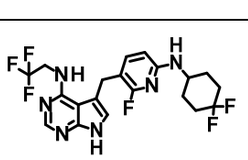
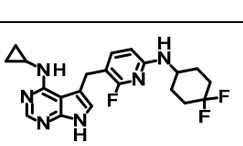
No.	Estructura del Compuesto	MS (ESI) $[M+H^+]^+$
P-4074		491.5
P-4075		448.0
P-4076		434.5
P-4077		450.0
P-4078		436.5
P-4079		452.0
P-4080		436.5
P-4081		408.5
P-4082		462.5
P-4083		394.5

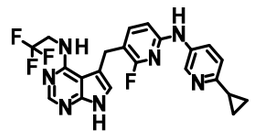
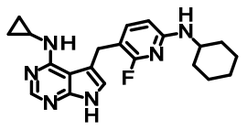
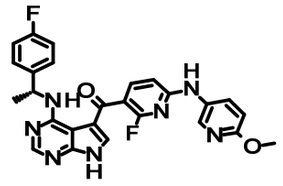
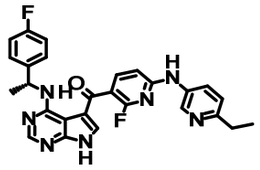
No.	Estructura del Compuesto	MS (ESI) $[M+H^+]^+$
P-4084		462.5
P-4085		406.0
P-4086		469.5
P-4087		455.2
P-4088		413.2
P-4089		387.2
P-4090		470.2
P-4091		458.0
P-4092		432.0

No.	Estructura del Compuesto	MS (ESI) $[M+H^+]^+$
P-4093		429.9
P-4094		403.9
P-4095		432.5
P-4096		496.5
P-4097		500.5
P-4098		450.0
P-4099		446.5
P-4100		434.5
P-4101		397.5

No.	Estructura del Compuesto	MS (ESI) $[M+H^+]^+$
P-4102		369.1
P-4103		462.1
P-4104		462.1
P-4105		422.0
P-4106		422.2
P-4107		420.2
P-4108		393.9
P-4109		412.9
P-4110		384.9

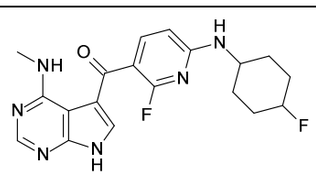
No.	Estructura del Compuesto	MS (ESI) $[M+H^+]^+$
P-4111		446.1
P-4112		446.0
P-4113		418.1
P-4114		406.0
P-4115		377.9
P-4116		462.1
P-4117		420.0
P-4118		432.2
P-4119		436.1
P-4120		460.1

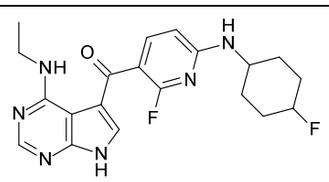
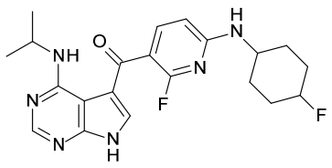
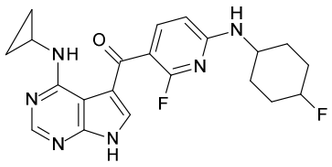
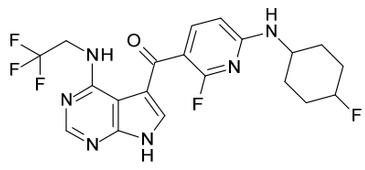
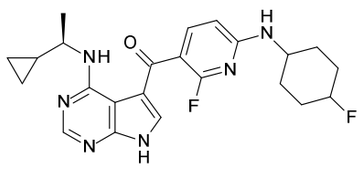
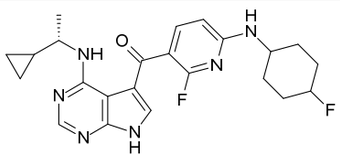
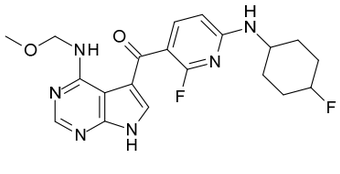
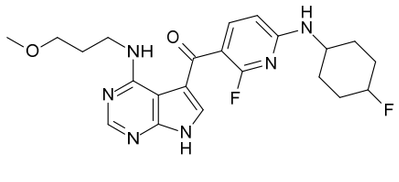
No.	Estructura del Compuesto	MS (ESI) $[M+H^+]^+$
P-4121		434.1
P-4122		420.0
P-4123		406.5
P-4124		391.9
P-4125		418.0
P-4126		420.0
P-4127		417.0
P-4128		459.0
P-4129		417.0

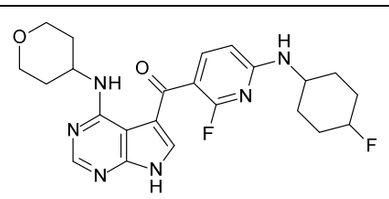
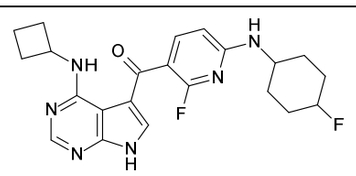
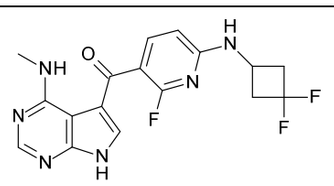
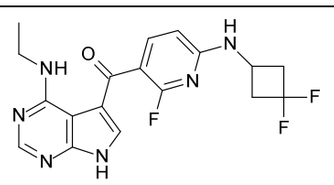
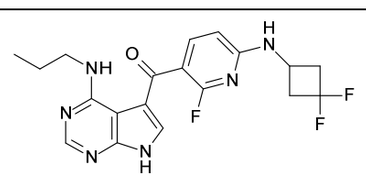
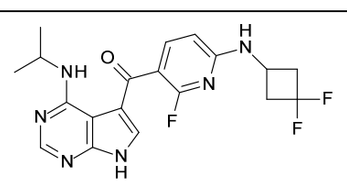
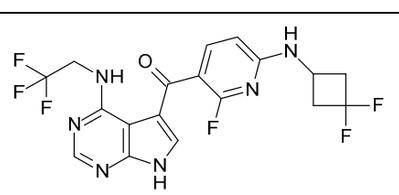
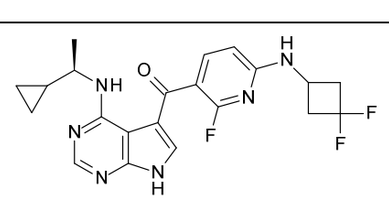
No.	Estructura del Compuesto	MS (ESI) $[M+H^+]^+$
P-4130		458.0
P-4131		379.0
P-4132		502.5
P-4133		500.5

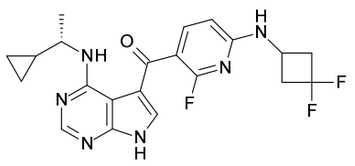
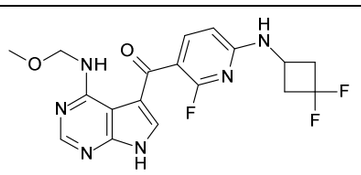
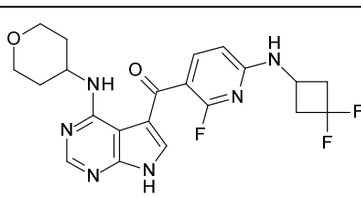
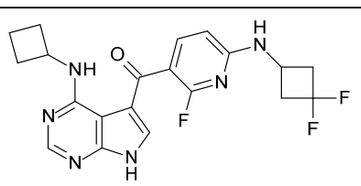
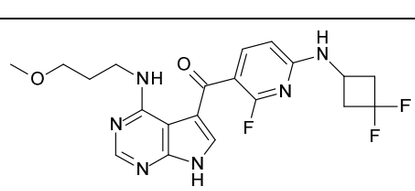
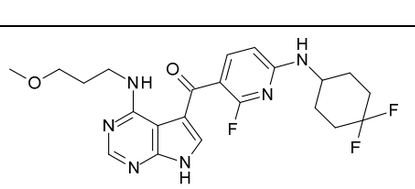
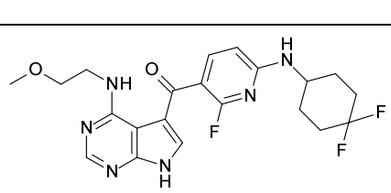
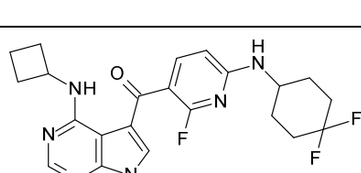
Los compuestos descritos en la Tabla 7 se preparan de acuerdo con los protocolos sintéticos establecidos en los Esquemas 14 y 15. Las estructuras son caracterizadas por espectroscopia de masa y espectroscopias de RMN de ^{1}H y ^{13}C.

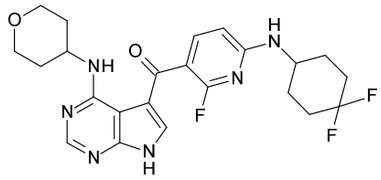
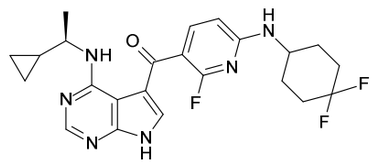
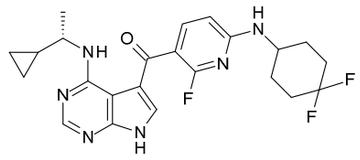
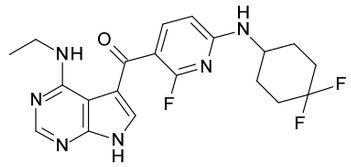
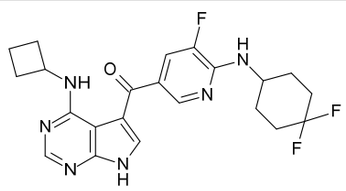
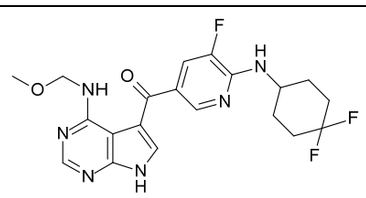
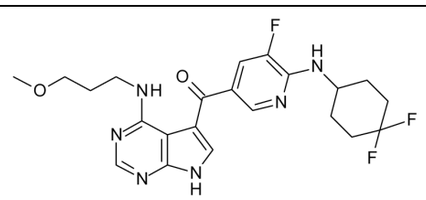
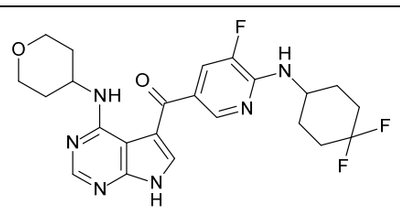
Tabla 7

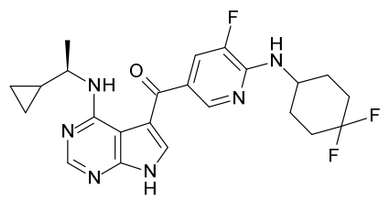
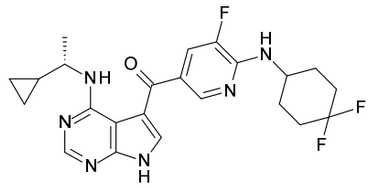
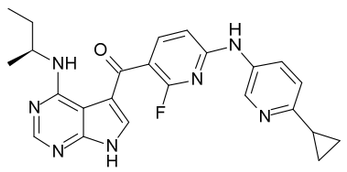
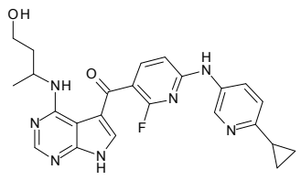
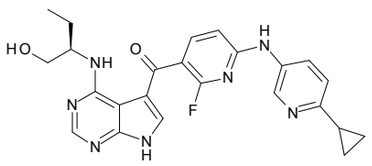
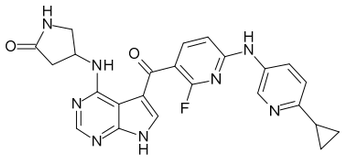
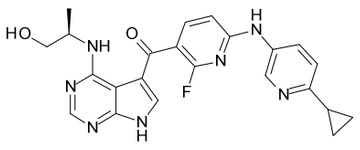
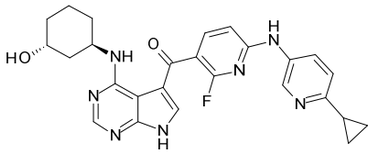
No	Nombre	Estructura
P-4134	[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]-[4-(metilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	

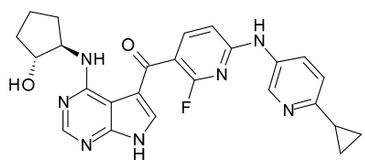
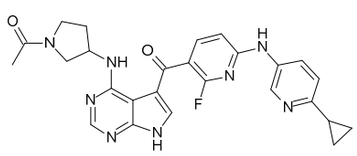
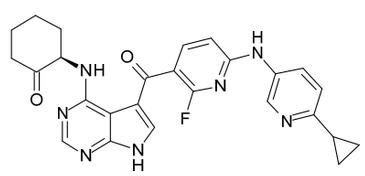
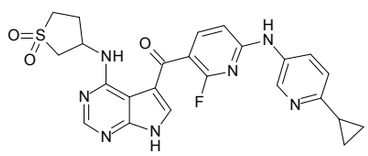
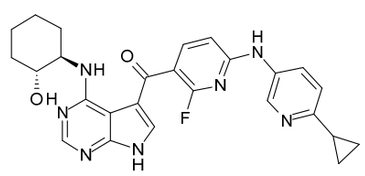
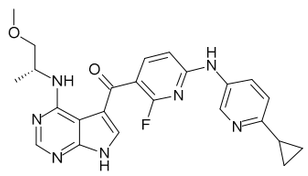
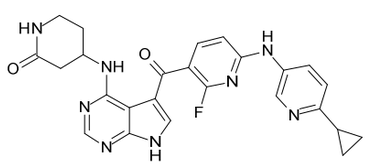
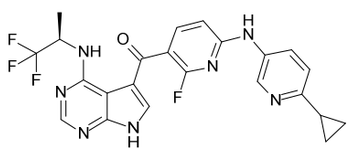
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P-4136	[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]-[4-(isopropilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4137	[4-(ciclopropilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]metanona	
P-4138	[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]-[4-(2,2,2-trifluoroetilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4139	[4-[[(1R)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]metanona	
P-4140	[4-[[(1S)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]metanona	
P-4141	[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]-[4-(metoximetilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4142	[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]-[4-(3-metoxipropilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	

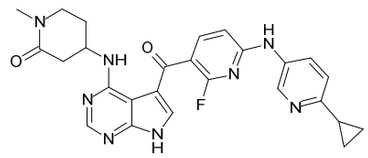
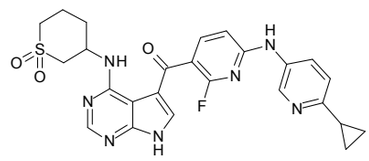
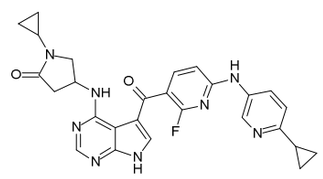
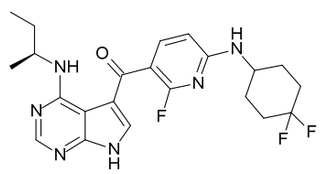
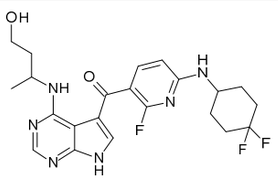
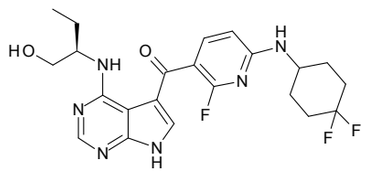
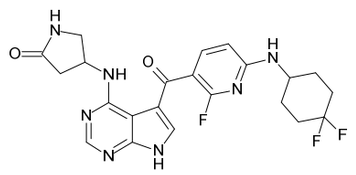
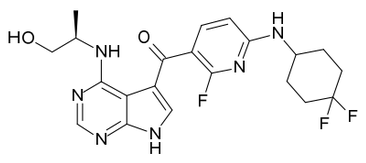
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P-4144	[4-(ciclobutilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]-[2-fluoro-6-[(4-fluorociclohexil)amino]-3-piridil]metanona	
P-4145	[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(metilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4146	[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(etilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4147	[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(propilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4148	[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(isopropilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4149	[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(2,2,2-trifluoroetilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4150	[4-[[(1R)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]metanona	

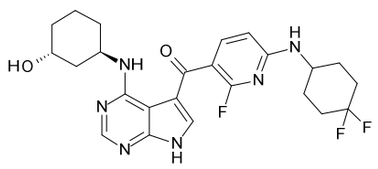
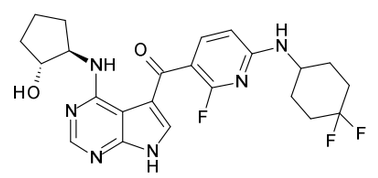
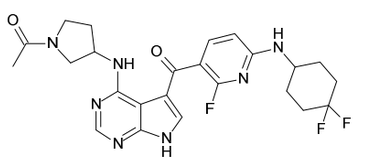
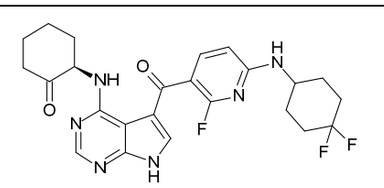
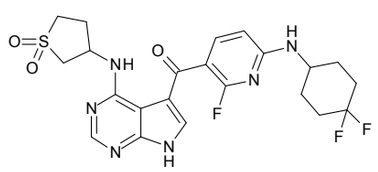
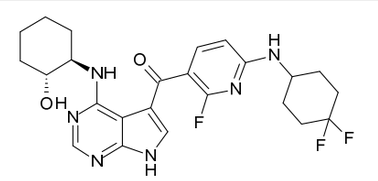
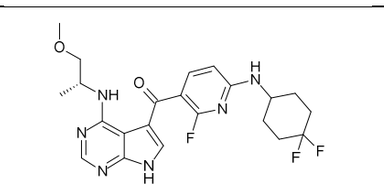
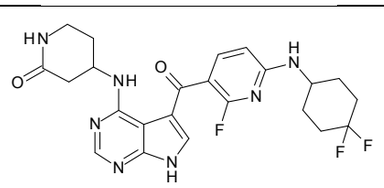
No	Nombre	Estructura
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P-4152	[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(metoximetilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4153	[6-[(3,3-15difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(tetrahidropiran-4-ilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4154	[4-(ciclobutilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]metanona	
P-4155	[6-[(3,3-difluorociclobutil)amino]-2-fluoro-3-piridil]-[4-(3-metoxipropilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4156	[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-(3-metoxipropilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4157	[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-(2-metoxietilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4158	[4-(ciclobutilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]metanona	

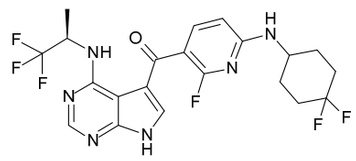
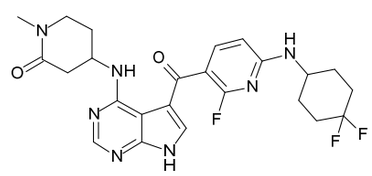
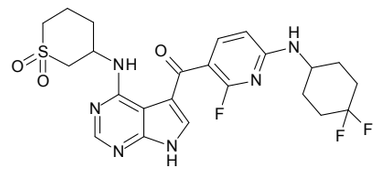
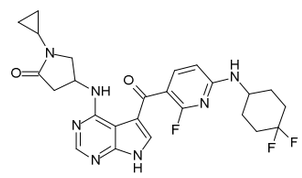
No	Nombre	Estructura
P-4159	[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-(tetrahidropiran-4-ilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4160	[4-[[(1R)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]metanona	
P-4161	[4-[[(1S)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]metanona	
P-4162	[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-(etilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4163	[4-(ciclobutilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]metanona	
P-4164	[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]-[4-(metoximetilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4165	[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]-[4-(3-metoxipropilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4166	[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]-[4-(tetrahidropiran-4-ilamino)-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	

No	Nombre	Estructura
P-4167	[4-[[(1R)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]metanona	
P-4168	[4-[[(1S)-1-ciclopropiletil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]-[6-[(4,4-difluorociclohexil)amino]-5-fluoro-3-piridil]metanona	
P-4169	[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1S)-1-metilpropil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4170	[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[(3-hidroxi-1-metil-propil)amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4171	[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-1-(hidroximetil)propil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4172	4-[[5-[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]pirrolidina-2-ona	
P-4173	[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-2-hidroxi-1-metil-etil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4174	[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1R,3R)-3-hidroxiciclohexil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	

No	Nombre	Estructura
P-4175	[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1R,2R)-2-hidroxiciclopentil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4176	1-[3-[[5-[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]pirrolidina-1-il]etanona	
P-4177	(2R)-2-[[5-[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]ciclohexanona	
P-4178	[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[(1,1-dioxotiolan-3-il)amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4179	[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1R,2R)-2-hidroxiciclohexil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4180	[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-2-metoxi-1-metil-etil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4181	4-[[5-[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]piperidin-2-ona	
P-4182	[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-2,2,2-trifluoro-1-metil-etil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	

No	Nombre	Estructura
P-4183	4-[[5-[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]-1-metil-piperidin-2-ona	
P-4184	[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-3-piridil]-[4-[(1,1-dioxotian-3-il)amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4185	1-ciclopropil-4-[[5-[6-[(6-ciclopropil-3-piridil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]pirrolidina-2-ona	
P-4186	[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1S)-1-metilpropil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4187	[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[(3-hidroxi-1-metil-propil)amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4188	[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-1-(hidroximetil)propil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4189	4-[[5-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]pirrolidina-2-ona	
P-4190	[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-2-hidroxi-1-metil-etil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	

No	Nombre	Estructura
P-4191	[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1R,3R)-3-hidroxiciclohexil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4192	[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1R,2R)-2-hidroxiciclopentil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4193	1-[3-[[5-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]pirrolidina-1-il]etanona	
P-4194	(2R)-2-[[5-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]ciclohexanona	
P-4195	[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[(1,1-dioxotiolan-3-il)amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4196	[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1R,2R)-2-hidroxiciclohexil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4197	[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-2-metoxi-1-metil-etil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4198	4-[[5-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]piperidin-2-ona	

No	Nombre	Estructura
P-4199	[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[[(1R)-2,2,2-trifluoro-1-metil-etil]amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4200	4-[[5-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]-1-metil-piperidin-2-ona	
P-4201	[6-[(4,4-difluorociclohexil)amino]-2-fluoro-3-piridil]-[4-[(1,1-dioxotian-3-il)amino]-7H-pirrolo[2,3-d]pirimidina-5-il]metanona	
P-4202	1-ciclopropil-4-[[5-[6-[(4,4-difluorociclohexil)amino]-2-fluoro-piridina-3-carbonil]-7H-pirrolo[2,3-d]pirimidina-4-il]amino]pirrolidina-2-ona	

Ejemplo 16: Propiedaes del Compuesto

[0719] Mientras la actividad inhitoria de los compuestos de cuaquier quinasa Fms, Kit, Flt-3, TrkA, TrkB y TrkC es importante para su actividad al tratar enfermedades, los compuestos aquí descritos muestran propiedades favorables que brindan también ventajas farmacéuticas. En algunos casos, la selectividad de la Fms relativa a la Kit y otras quinasas brinda una actividad preferida al tratar ciertas enfermedades, tales como artritis reumatoide, Enfermedad de Alzheimer, Enfermedad de Parkinson, osteoartritis, glomerulonefritis, nefritis intersticial, nefritis lúpica, necrosis tubular, nefropatía diabética, o hipertrofia renal. En algunos casos, la selectividad de los compuestos de la Fms en combinación con la

incapacidad de los compuestos de cruzar la barrera sangre-cerebro brinda una actividad preferida al tratar ciertas enfermedades como osteoartritis, glomerulonefritis, nefritis intersticial, nefritis lúpica, necrosis tubular, nefropatía diabética, o hipertrofia renal. En algunos casos, la selectividad de la Fms de los compuestos en combinación con la capacidad de los compuestos de cruzar efectivamente la barrera sangre-cerebro brinda una actividad preferida al tratar ciertas enfermedades como artritis reumatoide, Enfermedad de Alzheimer, o Enfermedad de Parkinson. En algunos casos, la actividad dual de la Fms/Kit brinda una actividad preferida al tratar ciertas enfermedades como cáncer de seno, cáncer de próstata, mieloma múltiple, melanoma, leucemia mieloide aguda, gliobastoma, metastásis cerebral, neurofibromatosis, tumores estromales gastrointestinales, artritis reumatoide y esclerosis múltiple. En algunos casos, la actividad dual de la Fms/Flt-3 brinda una mejor actividad al tratar ciertas enfermedades como leucemia mieloide aguda. En adición, al demostrar la actividad inhibitoria de la quinasa contra la Fms, Kit, Flt-3 o al menos la Fms y Kit o Fms y Flt-3 en ensayos con base bioquímica y celular, los compuestos han mejorado la solubilidad, las propiedades farmacocinéticas y han disminuido la inhibición del Cyp. Los compuestos se evalúan en los siguientes ensayos o ensayos similares disponibles para aquellos versados en el arte.

[0720] Los ensayos de actvividad con base bioquímica o célulaular son bien conocidos en el arte, por Ejemplo, La Publicación de la Aplicación de la Patente Estadounidense Número 2009/0076046, cuya divulgación se incorpora aquí por referencia ya que se relaciona con dichos ensayos- Por ejemplo, en un ensayo de la actividad bioquímica se determinan los valores del CI50 con respecto a la inhibición

de la actividad de la quinasa c-Kit, donde la inhibición de la fosforilización de sustrato péptido se mide como función de la concentración del compuesto. Los compuestos que serán probados se disuelven en DMSO a una concentración de 20 mM. Estos se diluyen a 30 µL en 120 µL de DMSO (4 mM) y se añade 1 µL a una placa de ensayo. Luego se diluyen serialmente 1:2 (50 µL a 100 µL de DMSO) para un total de 8 puntos. Se preparan las placas para que cada reacción de quinasa sea de 20 µL en el búfer de quinasa 1x kinase (25 mM HEPES, pH 7.5, 2 mM $MgCl_2$, 2 mM $MnCl_2$, 0.01% Tween-20, 1 mM DTT, 0.01% BSA), 5% DMSO y 100 µM ATP. El sustrato es biotina 30 nM (E4Y)10 (Millipore). La quinasa C-kit (se obtiene a partir de Millipore (#14-559) o se prepara como se describe en la Públicación de la Patente Estadounidense Número 2009/0076046, cuya divulgación se incorpora aquí por referencia ya que se relaciona con este ensayo) y es de 0.75 ng por muestra. Después de la incubación de la reacción de la quinasa por 1 hora a temperatura ambiente, se añade 5 µL de microesferas donantes (microesferas recubiertas de Estreptavidina (Perkin Elmer Life Science) a una concentración final de 10 µg/mL) en amortiguador (25 mM Hepes , pH 7.5, 100 mM EDTA, 0.01% BSA), la muestra se mezcla y se incuba por 20 minutos a temperatura ambiente antes de añadir 5 µL de microesferas aceptoras (microesferas recubiertas PI20 (Perkin Elmer Life Science) a concentración final de 10 µg/mL) en amortiguador. Las muestras se incuban por 60 minutos a temperatura ambiente y se lee la señal por pozo en un lector Envision. El sustrato fosforilizado resulta en el enlace del anticuerpo PI20 y la asociación de las microesferas donantes y aceptoras para que la señal se correlacione con la actividad de la quinasa. Se usa la concentración señal vs. compuesto para determinar el CI_{50}.

[0721] En un ensayo los valores CI_{50} de actividad bioquímica se determinan con respect a la actividad de la quinasa Fms, donde la inhibición de la fosforilización de un sustrato péptido se mide como una función de la concentración del compuesto. Los compuestos que serán probados, disueltos en DMSO (1 µL), se añaden a placas de 384 pocillos blancos (Costar #3705). Se preparan stocks de operación de la quinasa Fms (Invitrogen #PV3249), sustrato de biotina-$(E4Y)_{10}$ (Upstate Biotech, Cat# 12-440), y ATP (Sigma, Cat#A-3377) en 25 mM Hepes, pH 7.5, 0.5 mM $MgCl_2$, 2 mM $MnCl_2$, 2 mM DTT, 0.01% BSA, y 0.01% Tween-20. Todos los componentes se añaden a la placa de 384 pocillos para un concentración final de 1 ng/pocillo de Fms, 30 nM de biotina$(E4Y)_{10}$ (Upstate Biotechnology) y 100 µM de ATP en un volumen de 20 µL. Cada muestra está en DMSO al 5%. Luego la placa se incuba por 20 minutos a 30 ^oC. Justo antes de entrar, los stocks de operación de las microesferas donantes y aceptoras a partir del Kit de Detección AlfaScreen PI20 (PerkinElmer, Cat#676601M) se preparan en 25 mM Hepes, pH 7.5, pH 7.4, 100 mM EDTA, 0.01% BSA. Para detener la reacción, se deja sin cubrir en la oscuridad y se añade 5 µL de Solución de Microesferas Donantes (microesferas de Estreptavidina) a cada pocillo. La placa se incuba a temperatura ambiente por 20 minutos. Luego se añaden a cada pocillo cinco microlitros de solución de microesferas aceptoras (microesferas recubiertas PI20). La concentración final de cada pocillo es de 10 µg/mL. Las placas son incubadas a temperatura ambiente por 60 minutos. Se registra la señal fluorescente en el lector Envision. El sustrato fosforilizado se enlaza con el anticuerpo PI20 en asociación con las microesferas donantes y aceptoras para que la señal se correlacione con la actividad de la quinasa. Se usa la concentración señal vs. compuesto para determinar el CI_{50}.

[0722] En un ensayo los valores CI_{50} de actividad bioquímica se determinan con respect a la actividad de la quinasa Flt-3, donde la inhibición de la fosforilización de un sustrato péptido se mide como función de la concentración del compuesto. Los compuestos que serán probados, disueltos en DMSO (1 µL), se añaden a 384 pocillos blancos (Costar #3705). Los stocks de operación de la quinasa Flt-3 kinase (Invitrogen), biotina-$(E4Y)_{10}$ substrate (Upstate Biotech, Cat# 12-440), y ATP (Sigma, Cat#A-3377) se preparan en 25 mM Hepes f 7.5, 5 mM $MgCl_2$, 5 mM $MnCl_2$, 1 mM DTT, y 0.01% Tween-20. Todos los componentes se añaden a la placa de 384 pocillos para una concentración final de 1 ng/pocillo de Flt-3, 30 nM de biotina-$(E4Y)_{10}$ y 100 µM ATP en un volumen de 20 µL. Cada muestra está en DMSO al 5%. Luego la placa se incuba por 1 hora a temperatura ambiente. Justo antes de usar, los stocks de operación de las microesferas donantes y aceptoras a partir del Kit de Detección AlfaScreen PI20 (PerkinElmer, Cat#676601M) se preparan en 25 mM Hepes, pH 7.5, pH 7.4, 100 mM EDTA, 0.3% BSA. Para detener la reacción, la placa se deja sin cubrir en la oscuridad y se añade 5 µL de Solución de Microesferas Donantes (microesferas de Estreptavidina) a cada pocillo. La placa se incuba a temperatura ambiente por 20 minutos. Luego se añaden a cada pocillo cinco microlitros de solución de microesferas aceptoras (microesferas recubiertas PI20). La concentración final de cada pocillo es de 10 µg/mL. Las placas son incubadas a temperatura ambiente por 60 minutos. Se registra la señal fluorescente en el lector Envision. El sustrato fosforilizado se enlaza con el anticuerpo PI20 en asociación con las microesferas donantes y aceptoras para que la señal se correlacione con la actividad de la quinasa. Se usa la concentración señal vs. compuesto para determinar el CI_{50}.

[0723] En un ensayo de actividad bioquímica se determinan los valores de actividad CI_{50} con respecto a la inhibición de la actividad dela quinasa TrkA, donde la inhibición de la fosforilización de un sustrato péptido se mide como función de la concentración del compuesto. Los compuestos que serán probados, disueltos en DMSO (1 μL), se añaden a 384 pocillos blancos (Costar #3705). Los stocks de operación de la quinasa TrkA (UBI), el sustrato de biotina-$(E4Y)_{10}$ (Upstate Biotech, Cat# 12-440), y ATP (Sigma, Cat#A-3377) se preparan en 25 mM Hepes f 7.5, 10 mM $MnCl_2$, 1 mM DTT, 0.01 % BSA, y 0.01% Tween-20. Todos los componentes se añaden a la placa de 384 pocillos para una concentración final de 1 ng/pozo de TrkA, 30 nM de biotina-$(E4Y)_{10}$ y 100 μM ATP en un volumen de 20 μL. Cada muestra está en DMSO al 5%. La placa se agita por 1 minuto a 1200 rpm, se gira 1 minuto a 1000 rpm, luego se incuba por 40 minutos a temperatura ambiente. Justo antes de usar, los stocks de operación de las microesferas donantes y aceptoras a partir del Kit de Detección AlfaScreen PI20 (PerkinElmer, Cat#676601M) se preparan en 25 mM Hepes, pH 7.5, pH 7.4, 100 mM EDTA, 0.01% BSA. Para detener la reacción, la placa se deja sin cubrir en la oscuridad y se añade 5 μL de Solución de Microesferas Donantes (microesferas de Estreptavidina) a cada pocillo. La placa se incuba a temperatura ambiente por 20 minutos. Luego se añaden a cada pocillo cinco microlitros de solución de microesferas aceptoras (microesferas recubiertas PI20). La concentración final de cada pocillo es de 10 μg/mL. Las placas son incubadas a temperatura ambiente por 20 minutos. Se registra la señal fluorescente en el lector Envision. El sustrato fosforilizado se enlaza con el anticuerpo PI20 en asociación con las microesferas donantes y aceptoras para que la señal se correlacione con la actividad de la quinasa. Se usa la

concentración señal vs. compuesto para determinar el CI_{50}. Se usan ensayos similares para las quinasas TrkB y Trk C.

[0724] Los compuestos son evaluados en distintos ensayos celulares. Por ejemplo las células BaF3 diseñadas con BCR-FMS, BCR-KIT, BCR-FLT3, BCR-NTRK1, BCR-NTRK2, y BCR-NTRK3, se usan para los ensayos de proliferación celular para evaluar la actividad inhibitoria de las quinasas Fms, Kit, Flt-3, TrkA, TrkB, y TrkC, respectivamente. Se usa un ensayo de proliferación celular de MV-4-11 (leucemia) para evaluar la actividad inhibitoria de la quinasa Flt-3, y se us el ensayo de prolieración celular de SKNSH (neuroblastoma humano) para evaluar la eficacia de los inhibidores de las quinasas Fms/Trk. Las células adicionales pueden ensayarse de forma similar para evaluar la eficaci de los inhibidores de las quinasas Fms/Trk, such tales como las células MiaPaCa (cáncer pancreático humano) y Capan-1 (carcinoma pancreático humano). El reactivo y las condiciones del ensayo son las siguientes:

Células BaF3:

Mantenidas en RPMI que contiene 10% FBS, 1% PenStrep, 1% NEAA, y 1% L-Glutamina, suplementada con 1 mg/mL G418 y 5% WEHI-CM (o murina recombinante IL-3).

Las células confluentes se dividen en 1:50 a 1:100 cada 3-4 días.

Células MV-4-11:

Mantenidas en Medio Modificado de Dulbecco de Iscove que contiene 10% FBS.

Las células confluentes se dividen en 1:4 cada 3-4 días.

Células SKNSH: RPMI que contiene 10% FBS.

Las células se cuentan en el día 1, luego se centrifugan en un tubo cónico por 5 minutos a 1000 rpm. Se remueve el sobrenadante y las células se suspenden nuevamente así:

BaF3: resuspendido en medio de crecimiento + 1 mg/mL G418 (sin WEHI/IL-3) a 2 x 10^5 células/mL.

MV-4-11: resuspendido en medio de crecimiento a 5 x 10^5 células/mL.

SKNSH: resuspendido en medio de crecimiento a 2 x 10^4 células/mL.

Las células son colocadas en una placa (de 50 µL, 150 µL para células SKNSH) en cada pocillo del disco de 96 pocillos (Corning 3610) y se incuban a 37 ^oC en CO_2 al 5% toda la noche, las células se colocan en placa a una concentración final así:

BaF3: 10,000 células por pocillo.

MV-4-11: 25,000 células por pocillo.

SKNSH: 3,000 células por pocillo.

En el día 2, el compuesto se diluye 1:3 a una concentración maxima de 5 mM para un total de 8 puntos de titulación con DMSO como control. Se añade una alicuota de 1 µL de cada punto de dilución al medio de crecimiento de 249 µL y se añade 50 µL al pocillo que contiene las células, suministrando un compuesto de 10 µM para el punto máximo de concentración. Las células se incuban por 3 días a 37 ^oC en CO_2 al 5%. Para las células SKNSH, se añade una alicuota de 0.75 µL de dilución apropiada en DMSO a 150 µL de células.

En el día 5, se lleva a temperatura ambiente un Sistema de Ensayo de Luminicencia ATPlite de 1 Paso (Perkin Elmer # 6016739) junto con los cultivos celulares. Se añade ATPlite a cada pocillo así:

BaF3: 25 μL por pocillo.

MV-4-11: 40 μL por pocillo.

SKNSH: 20 μL por pocillo.

Las células se incuban a temperatura ambiente por 10 minutos, luego se lee la luminicencia en el lector Safire. La luminicencia medida se correlaciona directamente con el número de células, para que se use la lectura como una función de la concentración del compuesto para determinar el valor CI_{50}.

[0725] Además, se usa un ensayo de diferenciación osteoclástica para evaluar la eficacia de los inhibidores al trarta enfermedades oseas como osteoartritis. En el día 0, Se deshiela un Medio Osteoclástico BulletKit (Lonza catálogo # PT-8001, que contiene el Medio, FBS, L-Glutamina, PenStrep, RANKL, y M-CSF) y la FBS, L-glutamina y PenStrep del kit se añaden a 100 mL del Medio Basal Osteoclástico Precursos para proporcionar el Medio de Crecimiento de Precursores Osteoclásticos (OPGM). Este se calienta a 37 ^{o}C. Las células precursoras osteoclásticas (Lonza catálogo # 2T-110) congeladas en un criofrasco se calientan a 37 ^{o}C y se transiferene a un tubo cónico. El criofrasco se enjuaga con OPGM y se añade gota a gota al tubo cónico de las células con agitación, luego se ajusta el volumen a 20-30 mL con adición del OPGM. Las células son centrifugadas a 200 x g por 15 minutos a temperatura ambiente y todo menos aproximadamente 3 mL de sobrenadante se lleva a un nuvo tubo cónico. Las células se suspenden en el sobrenadante restante y el volume se ajusta a 10-15 mL con OPGM añadido gota a gota con agitación. Las células se centrifugan a 200 x g por 15 minutos a temperatura ambiente y todo menos aproximadamente 1 mL de supernadante se remueve. Las células son suspendidas nuevamente en el sobrenadante restante, contado, y el volumen se

ajusta con una cantidad apropiada de OPGM para proporcionar aproximadamente 1 x 10^5 de células/mL. Una alicuota de 0.1 mL se añade a cada pocillo de la placa de 96 pocillos. El compuesto que será probado se prepara en DMSO para platato a alta concentración de 2.5 mM, con diluciones seriales de 1:3 de 8 puntos. Se añade una alícuota de 1 µL de cada dilución del compuesto a una placa de polipropileno con fondo en v de 96 pocillos y se añade 0.124 mL de OPGM al compuesto. Luego se añade 50 µL del compuesto en OPGM a la placa de 96 pocillos con las células precursoras oteoclásticas (suministrando la mayor concentración de prueba de 5 µM). El RANKL (2 µg) a partir del BulletKit se reconstituye en 1 mL de OPGM, luego se mezcla en vórtex y se centrifuga brevemente. Se añade una alícuota de 792 µL de RANKL a 6 mL de OPGM y se añade 50 µL a los pozos de control. Luego se añade 76.6 µL **de** M-CSF (10 µg/mL) a partir del BulletKit a los 5.8 mL restantes de las solución de OPGM/RANKL (4X RANKL/M-CSF/OPGM). Se añade una alícuota de 50 µL a los pozos restantes, y el restante se almacena a 4 ^oC para uso posterior. La placa se incuba a 37 ^oC por 6 días, luego la solución restante de OPGM/RANKL/M-CSF se calienta a 37 ^oC. El restante de aproximadamente 198 µL se combina con 6 mL de OPGM. El medio se aspira a partir de los pocillos osteoclásticos y se añade 100 µL de RANKL/OPGM a los controles bajos. La solución de RANKL/OPGM se combina con approximadamente 18.5 µL de M-CSF restante. La solución restante 4X RANKL/M-CSF/OPGM a partir de día 0 se diluye a 1X y se combina con la solución recién preparada. Se añade una alícuota de 0.1 mL a cada pocillo osteoclástico y se incuba a 37 ^oC por 1 día. El Kit de Fosfatasa Ácida (Cayman Chemical Catálogo # 10008051) se calienta a temperatura ambiente. El búfer de ensayo se diluye a 5 mL con 45 mL de agua. Para cada placa, se disuelven dos tabletas de sustrato en 4.5 mL del búfer de ensayo, mezclando con

agitación en vórtex para romper la tableta. La solución amortiguadora se diluye con a 12 mL con 36 mL de agua. En una campana de cultivo celular, se transfieren 20 µL de sobrenadante de cada pocillo osteoclástico a la placa de 96 pocillos. Una alicuota de 30 µL de la solución del sustrato se añade a cada pocillo y se incuba a 37 ^{o}C por 20 minutos, luego se añaden 100 µL de solución amortiguadora a cada pocillo. La absorbencia de cada pozo se lee a 405 nM en el lector de placas Safire. La lectura de absorbencia se gráfica vs. la concentration para proporcionar el CI_{50} de cada compuesto.

[0726] Se entiende que los resultados de estos ensayos puede variar a medida que cambian las condiciones del ensayo. Los niveles de inhibición determinados bajo las condiciones aquí descritas representan la actividad relativa de los compuestos probados bajo las condiciones específicas empleadas. Los ensayos con base celular probablemente mostrarán variabilidad debido a la complejidad del sistema y la sensibilidad del mismo a cualquier cambio en las condiciones de ensayo. Como tal, algunos niveles de inhibición de los ensayos con base celular son indicación de que los compuestos tienen alguna actividad inhibitoria de dichas células, donde la falta de inhibición menor o igual al umbral de la mayor concentración probada no indica necesariamente que el compuesto no tenga actividad inhibitoria en la células, solo que bajo las condiciones probadas, no se observó ninguna inhibición. Los resultados de los compuestos probados y que no muestran ninguna inhibición sustancial por debajo de la mayor concentración probada son representados como "-" en las siguientes tablas. En algunos casos, los compuestos no fueron probados en todos los ensayos o los resultados del ensayo no fueron validos, como lo índica NA en las siguientes tablas.

[0727] La siguiente tabla indicates la actividad inhibitoria bioquímica de las quinasas Fms, Kit, Flt3, TrkA, y TrkC para los compuestos ejemplares indicados:

# Compuesto	Inhibición Bioquímica CI_{50} (μM)				
	Fms	Kit	Flt3	TrkA	TrkC
P-3049	< 0.1	< 1	NA	NA	NA
P-3051	< 1	> 1	NA	NA	NA
P-3052	< 0.01	< 1	> 1	NA	NA
P-3005	< 1	> 1	NA	NA	NA
P-3006	< 0.01	< 1	NA	NA	NA
P-3007	< 1	> 1	NA	NA	NA
P-3008	< 0.1	< 1	NA	NA	NA
P-3009	< 0.1	NA	NA	NA	NA
P-3010	< 0.01	< 0.1	< 0.1	< 1	NA
P-3059	< 0.01	< 0.01	< 0.01	> 1	NA
P-3060	< 0.01	< 0.01	< 0.1	> 1	NA
P-3061	< 0.01	< 1	> 1	NA	NA
P-3014	< 0.01	< 0.1	< 1	> 1	NA
P-3063	< 0.01	< 1	< 0.1	> 1	NA
P-3064	< 0.1	< 0.1	< 0.1	> 1	NA
P-3017	< 0.1	< 1	< 0.1	> 1	NA
P-3018	< 0.01	< 0.01	< 0.01	< 1	NA
P-3019	< 0.01	< 1	< 1	< 0.1	< 0.1

P-3020	< 0.01	< 0.01	< 0.01	< 0.1	< 1
P-3021	< 0.01	< 0.01	< 0.01	< 0.1	< 1
P-3022	< 0.1	< 0.1	< 0.1	< 1	< 1
P-3023	< 0.1	< 0.1	NA	NA	NA
P-3024	< 0.1	< 0.01	< 0.01	< 1	> 1
P-3025	< 0.1	< 0.01	< 0.01	< 0.1	< 0.01
P-3026	< 0.01	< 0.01	< 0.1	> 1	< 0.1
P-3027	< 0.01	< 0.01	< 0.01	< 1	< 0.1
P-3028	> 1	< 1	NA	< 0.1	< 0.1
P-3029	< 0.1	< 1	NA	< 1	< 1
P-3030	< 0.1	< 0.1	NA	< 0.01	< 0.01
P-3031	< 1	< 0.1	NA	< 0.1	< 0.1
P-3032	> 1	< 1	NA	> 1	> 1
P-3033	< 0.1	< 0.01	NA	< 0.01	< 0.1
P-3034	< 0.1	< 0.1	NA	< 1	< 1
P-3035	< 1	< 0.1	< 0.1	< 1	< 1
P-3036	< 0.01	< 0.1	< 0.1	< 1	< 1
P-3037	> 1	< 1	NA	NA	NA
P-3038	< 1	< 1	NA	NA	NA
P-3039	< 0.01	< 0.1	< 0.1	< 0.1	NA
P-3040	< 0.1	> 1	< 0.1	< 0.01	NA
P-3041	< 0.01	< 1	< 1	< 1	NA
P-3042	< 0.01	< 0.1	< 1	< 0.1	NA
P-3043	< 0.01	< 1	< 1	< 0.1	NA

P-3044	< 0.01	< 1	< 1	< 0.1	NA
P-3045	< 0.01	< 1	< 0.1	< 0.01	NA
P-3048	< 0.01	< 0.1	NA	< 0.01	NA
P-3049	< 0.01	< 0.1	NA	< 0.01	NA
P-3050	< 0.1	< 0.1	NA	< 0.1	NA
P-3051	< 0.01	< 0.1	NA	< 0.01	NA
P-3052	< 0.1	< 0.1	NA	< 0.01	NA
P-3053	< 0.01	< 0.1	NA	< 0.1	NA
P-4049	< 0.01	< 1	< 1	< 0.1	< 0.01
P-4050	< 0.1	< 1	NA	< 0.1	< 1
P-4051	< 0.1	< 1	< 1	< 1	NA
P-4052	< 0.1	< 0.1	< 0.01	< 0.1	NA
P-4005	< 0.01	< 0.1	< 0.1	< 0.1	NA
P-4006	< 0.01	< 0.1	< 0.1	< 0.1	NA
P-4007	< 0.01	< 0.1	< 0.1	< 0.01	NA
P-4008	< 0.01	< 1	< 0.1	< 0.01	NA
P-4009	< 0.01	< 0.1	< 0.1	< 0.01	NA
P-4010	< 0.01	< 1	< 1	< 1	NA
P-4059	< 0.01	< 1	< 1	< 1	NA
P-4060	< 0.01	< 1	< 1	< 0.1	NA
P-4061	< 0.01	< 1	> 1	< 1	NA
P-4014	< 0.01	< 0.1	< 1	> 1	NA
P-4063	< 0.1	< 0.1	> 1	> 1	NA
P-4064	< 0.01	< 0.1	< 0.01	< 0.01	NA

P-4017	< 0.01	< 0.1	< 0.1	< 0.1	NA
P-4018	< 0.01	< 0.1	< 0.1	< 0.1	NA
P-4019	< 0.01	< 1	< 0.1	< 0.1	NA
P-4020	< 0.01	< 0.1	< 0.1	< 0.01	NA
P-4021	< 0.1	< 1	> 1	< 1	NA
P-4022	< 0.1	< 1	< 0.1	< 0.01	NA
P-4023	< 0.01	< 1	< 1	< 0.1	NA
P-4024	< 1	< 1	< 0.1	< 0.1	NA
P-4025	< 1	> 1	< 1	< 0.1	NA
P-4026	< 0.01	< 1	< 0.1	< 0.01	NA
P-4027	< 0.1	< 0.1	< 0.01	< 0.01	NA
P-4028	< 0.01	< 0.1	< 0.1	< 0.01	NA
P-4029	< 0.01	< 0.1	< 0.01	< 0.01	NA
P-4030	< 0.01	< 1	< 1	< 0.1	NA
P-4031	< 0.1	< 0.1	< 0.1	< 0.1	NA
P-4032	< 0.1	< 0.1	< 0.1	< 0.1	NA
P-4036	< 0.01	< 1	> 1	< 0.1	NA
P-4037	< 0.1	< 1	< 1	< 0.1	NA
P-4038	< 0.1	< 1	NA	< 0.1	NA
P-4039	< 1	< 1	NA	< 0.1	NA
P-4040	< 0.1	< 0.1	NA	< 0.01	NA
P-4041	< 0.1	< 0.1	NA	< 0.01	NA
P-4046	< 0.1	< 1	NA	< 1	NA
P-4047	> 1	> 1	NA	>1	NA

P-4048	< 0.01	< 0.01	NA	< 0.01	NA
P-4049	< 0.01	< 1	NA	< 0.01	NA
P-4050	< 1	< 1	NA	< 1	NA
P-4051	< 1	< 1	NA	< 0.01	NA
P-4052	< 1	> 1	NA	< 1	NA
P-4053	< 0.01	< 1	NA	< 0.01	NA
P-4054	< 0.01	> 1	NA	< 0.1	NA
P-4055	< 0.1	< 1	NA	NA	NA
P-4056	< 0.1	< 0.1	NA	NA	NA
P-4057	< 0.1	> 1	NA	< 1	NA
P-4058	< 0.1	> 1	NA	< 1	NA
P-4059	< 0.1	< 1	NA	< 0.1	NA
P-4060	< 0.01	< 0.1	NA	< 0.01	NA
P-4061	< 0.1	> 1	NA	< 0.1	NA
P-4062	< 0.01	< 0.1	NA	< 0.01	NA
P-4063	< 0.01	< 1	NA	< 0.01	NA
P-4064	< 0.01	< 0.1	NA	< 0.01	NA
P-4065	< 0.01	< 0.1	NA	< 0.01	NA
P-4066	< 0.01	< 0.1	NA	< 0.01	NA
P-4067	< 0.01	< 1	NA	< 0.01	NA
P-4068	< 0.01	< 0.1	NA	< 0.01	NA
P-4069	< 1	> 1	NA	< 0.1	NA
P-4070	> 1	> 1	NA	> 1	NA
P-4071	< 1	> 1	NA	< 0.01	NA

P-4072	< 0.1	> 1	NA	< 0.1	NA
P-4073	< 0.1	< 1	NA	< 0.01	NA
P-4074	< 0.1	< 1	NA	< 0.01	NA
P-4075	< 0.01	< 1	NA	< 0.01	NA
P-4076	< 0.01	< 0.1	NA	< 0.01	NA
P-4077	< 0.1	< 1	NA	< 0.01	NA
P-4078	< 0.01	< 1	NA	< 0.01	NA
P-4079	< 0.01	< 0.1	NA	< 0.01	NA
P-4080	< 0.01	< 1	NA	< 0.01	NA
P-4081	< 0.01	< 0.1	NA	< 0.01	NA
P-4082	< 0.1	< 1	NA	< 0.01	NA
P-4083	< 0.01	< 0.1	NA	< 0.01	NA
P-4084	< 0.01	< 0.1	NA	< 0.01	NA
P-4085	< 0.01	< 1	NA	< 0.01	NA
P-4086	< 1	< 1	NA	< 0.1	NA
P-4087	< 0.1	< 0.1	NA	< 0.01	NA
P-4088	< 0.1	< 1	NA	< 0.01	NA
P-4089	< 0.1	< 1	NA	< 0.1	NA
P-4090	< 0.1	< 1	NA	< 0.1	NA
P-4091	< 0.1	< 0.1	NA	< 0.01	NA
P-4092	< 0.01	< 0.1	NA	< 0.01	NA
P-4093	< 0.01	< 0.1	NA	< 0.01	NA
P-4094	< 0.01	< 0.01	NA	< 0.01	NA
P-4095	< 0.01	< 0.1	NA	< 0.01	NA

P-4096	< 0.1	< 1	NA	< 0.1	NA
P-4097	< 1	< 1	NA	< 0.1	NA
P-4098	< 0.01	< 0.1	NA	< 0.01	NA
P-4099	< 0.1	< 0.1	NA	< 0.1	NA
P-4100	< 0.1	< 0.1	NA	< 0.1	NA
P-4101	< 0.1	< 1	NA	< 0.1	NA
P-4102	< 0.1	< 1	NA	< 0.1	NA
P-4103	< 1	< 1	NA	< 0.1	NA
P-4104	< 1	< 1	NA	< 0.1	NA
P-4105	< 0.1	> 1	NA	< 0.1	NA
P-4106	< 0.1	< 1	NA	< 0.01	NA
P-4107	< 0.1	< 0.1	NA	< 0.01	NA
P-4108	< 0.1	< 1	NA	< 0.1	NA
P-4109	< 0.1	< 1	NA	< 0.1	NA
P-4110	< 0.1	< 1	NA	< 1	NA
P-4111	< 0.1	< 1	NA	< 0.1	NA
P-4112	< 0.1	< 1	NA	< 0.1	NA
P-4113	< 0.01	< 0.1	NA	< 0.01	NA
P-4114	< 0.01	< 0.1	NA	< 0.01	NA
P-4115	< 0.01	< 0.1	NA	< 0.01	NA
P-4116	< 0.1	< 0.1	NA	< 0.01	NA
P-4117	< 0.01	< 0.1	NA	< 0.01	NA
P-4118	< 0.1	< 0.1	NA	< 0.01	NA
P-4119	< 0.01	< 0.01	NA	< 0.01	NA

P-4120	< 0.1	< 0.1	NA	< 0.1	NA
P-4121	< 0.1	< 0.01	NA	< 0.1	NA
P-4122	< 0.01	< 0.01	NA	< 0.01	NA
P-4123	< 0.01	< 0.01	NA	< 0.01	NA
P-4124	< 0.01	< 0.01	NA	< 0.01	NA
P-4125	< 0.1	< 0.1	NA	< 0.01	NA
P-4126	< 0.01	< 0.1	NA	< 0.01	NA
P-4127	< 0.1	< 1	NA	< 0.1	NA
P-4128	< 0.1	> 1	NA	< 1	NA
P-4129	< 0.1	< 1	NA	< 1	NA
P-4130	< 0.01	< 1	NA	< 0.01	NA

[0728] La siguienteTabla indica la inhibición de la proliferación celular de las células BCR-FMS, BCR-KIT, BCR-FLT3, BCR-NTRK1, BCR-NTRK2 y BCR-NTRK3 BaF3, las células MV-4-11 y las células SKNSH de los compuestos ejemplares indicados:

# Compuesto	Inhibición de la Proliferación Celular CI_{50} (μM)						
	BCR/BaF3					MV-4-11	SKNSH
	Fms	Kit	TrkA	TrkB	TrkC		
P-3049	< 0.1	> 1	-	-	-	NA	NA
P-3051	< 1	> 1	NA	NA	NA	NA	NA
P-3052	< 0.1	> 1	< 10	< 10	< 10	< 10	NA
P-3005	< 1	> 1	-	-	-	NA	NA

P-3006	< 1	> 1	< 20	-	-	NA	NA
P-3007	< 1	-	-	-	-	NA	NA
P-3008	< 0.1	> 1	NA	NA	NA	NA	NA
P-3009	< 1	> 1	-	-	-	NA	NA
P-3010	< 0.1	< 1	-	-	-	NA	NA
P-3059	< 0.1	< 0.1	< 1	< 1	< 0.1	NA	NA
P-3060	< 0.1	< 1	< 1	< 1	< 1	NA	NA
P-3061	< 0.1	> 1	-	-	-	< 10	NA
P-3014	< 0.1	> 1	-	-	-	NA	NA
P-3063	< 1	> 1	-	-	-	NA	NA
P-3064	< 1	> 1	-	-	-	NA	NA
P-3017	< 1	> 1	-	-	-	NA	NA
P-3018	< 0.1	< 0.1	< 1	< 0.1	< 0.1	< 0.01	NA
P-3019	< 0.01	< 1	< 0.1	< 0.1	< 0.1	< 1	< 10
P-3020	< 0.01	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 1
P-3021	< 0.01	< 0.1	< 1	< 0.1	< 0.1	NA	< 1
P-3022	< 0.1	< 0.1	< 1	< 1	< 1	< 1	NA
P-3023	< 0.1	< 0.1	< 1	< 1	< 1	< 0.1	NA
P-3024	< 0.01	< 0.1	< 1	< 1	< 0.1	NA	< 1
P-3025	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	NA	< 1
P-3026	< 0.01	< 0.1	< 0.1	< 0.1	< 0.1	NA	-
P-3027	< 0.01	< 0.1	< 0.1	< 1	< 0.1	< 0.01	-
P-3028	< 1	< 0.1	< 0.1	< 1	< 0.1	NA	< 20
P-3029	< 0.1	< 1	> 1	> 1	< 1	NA	-

P-3030	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	NA	< 0.1
P-3031	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	NA	< 0.1
P-3032	< 1	< 1	< 1	> 1	< 1	NA	< 1
P-3033	< 0.01	< 0.01	< 0.1	< 0.1	< 0.1	NA	< 1
P-3034	< 0.01	< 0.1	< 0.1	< 1	< 0.1	NA	< 1
P-3035	< 0.1	< 1	< 1	< 1	< 0.1	< 1	< 1
P-3036	< 0.01	< 0.1	< 1	< 1	< 1	< 0.1	< 20
P-3037	> 1	> 1	> 1	-	> 1	NA	-
P-3038	< 1	< 1	< 1	> 1	< 1	> 1	-
P-3039	< 0.01	< 1	< 1	< 1	< 0.1	< 1	> 1
P-3040	< 0.1	> 1	< 0.1	< 0.01	< 0.01	NA	> 1
P-3041	< 0.01	< 1	< 1	< 1	< 0.1	NA	> 1
P-3042	< 0.1	< 1	< 1	< 0.1	< 0.1	NA	> 1
P-3043	< 0.1	< 1	< 0.1	< 0.1	< 0.1	NA	< 1
P-3044	< 0.1	< 1	< 1	< 0.1	< 0.1	NA	> 1
P-3045	< 0.1	< 1	< 0.1	< 0.01	< 0.1	NA	-
P-3048	< 0.01	< 0.1	< 0.1	NA	NA	NA	NA
P-3049	< 0.01	< 0.1	< 0.01	NA	NA	NA	NA
P-3050	< 0.1	< 1	< 0.1	NA	NA	NA	NA
P-3051	< 0.1	< 1	< 0.1	NA	NA	NA	NA
P-3052	< 0.1	NA	< 0.1	NA	< 0.01	NA	NA
P-3053	< 0.01	NA	< 0.1	NA	< 0.01	NA	NA
P-4049	< 0.01	< 1	< 0.1	< 0.1	< 0.01	< 1	< 1
P-4050	< 0.1	< 1	< 1	< 1	< 0.1	NA	< 0.1

P-4051	< 0.1	> 1	< 1	< 1	< 0.1	< 1	> 1
P-4052	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	< 1	< 1
P-4005	< 0.01	< 0.1	< 0.1	< 0.01	< 0.01	< 1	< 1
P-4006	< 0.01	< 0.1	< 0.1	< 0.01	< 0.01	< 0.1	< 0.1
P-4007	< 0.01	< 1	< 0.01	< 0.1	< 0.01	< 1	< 1
P-4008	< 0.01	< 1	< 0.1	< 0.1	< 0.1	< 0.1	> 1
P-4009	< 0.01	< 1	< 0.1	< 0.01	< 0.01	< 0.1	< 0.1
P-4010	< 0.01	< 1	< 1	< 0.1	< 0.1	< 1	< 1
P-4059	< 0.01	> 1	< 1	< 1	< 1	< 1	> 1
P-4060	< 0.01	< 1	< 1	< 0.1	< 0.1	< 1	> 1
P-4061	< 0.01	< 1	< 1	< 1	< 1	< 1	> 1
P-4014	< 0.1	> 1	< 1	< 1	< 1	< 1	> 10
P-4063	< 0.01	> 1	< 1	< 1	< 0.1	< 1	> 1
P-4064	< 0.01	< 0.1	< 0.1	< 0.01	< 0.01	< 0.1	> 1
P-4017	< 0.01	< 1	< 1	< 1	< 0.1	< 1	< 1
P-4018	< 0.01	< 1	< 0.1	< 0.1	< 0.01	< 1	< 1
P-4019	< 0.01	< 1	< 1	< 0.1	< 0.1	< 1	> 1
P-4020	< 0.1	< 1	< 1	< 0.1	< 0.1	NA	< 1
P-4021	< 1	> 1	> 1	< 1	< 1	NA	< 1
P-4022	< 0.1	< 1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4023	< 0.01	< 1	< 0.1	< 0.1	< 0.01	NA	< 1
P-4024	< 0.1	< 1	< 0.1	< 0.1	< 0.1	NA	> 1
P-4025	< 0.1	> 1	< 0.1	< 0.1	< 0.1	NA	> 1
P-4026	< 0.01	< 1	< 0.1	< 0.01	< 0.01	NA	NA

P-4027	< 0.1	< 1	< 0.1	< 0.01	< 0.01	NA	NA
P-4028	< 0.01	< 1	< 0.01	< 0.01	< 0.01	NA	NA
P-4029	< 0.1	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4030	< 0.01	< 1	< 1	< 0.1	< 0.1	NA	NA
P-4031	< 0.1	< 1	< 0.1	< 0.01	< 0.01	NA	NA
P-4032	< 0.1	< 1	< 0.1	< 0.1	< 0.1	NA	NA
P-4036	< 0.1	< 1	< 1	< 0.1	< 0.1	NA	NA
P-4037	< 0.1	< 0.1	< 0.1	NA	NA	NA	NA
P-4038	< 0.1	< 1	< 1	< 1	< 0.1	NA	NA
P-4039	< 0.1	< 1	< 0.1	< 0.1	< 0.1	NA	NA
P-4040	< 0.1	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4041	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4046	< 0.1	< 1	< 1	< 1	< 1	NA	< 10
P-4047	>1	> 1	> 1	> 1	> 1	NA	NA
P-4048	< 0.01	< 1	< 1	< 0.01	< 0.01	NA	< 1
P-4049	< 1	< 1	< 1	< 1	< 1	NA	< 1
P-4050	< 1	> 1	< 1	< 1	< 1	NA	< 1
P-4051	< 1	> 1	< 1	< 0.01	< 0.01	NA	< 1
P-4052	< 1	> 1	< 1	< 1	< 0.01	NA	> 1
P-4053	< 1	< 1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4054	< 1	< 1	< 1	< 1	< 0.01	NA	< 10
P-4055	< 1	> 1	< 1	< 0.01	< 0.01	NA	< 1
P-4056	< 1	> 1	< 1	< 0.01	< 0.01	NA	< 1
P-4057	< 1	> 1	> 1	> 1	< 1	NA	< 10

P-4058	< 0.1	< 1	< 1	< 1	< 0.1	NA	< 10
P-4059	< 0.1	> 1	< 1	< 0.1	< 0.1	NA	< 1
P-4060	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 0.1
P-4061	< 0.1	> 1	< 0.1	< 0.01	< 0.01	NA	NA
P-4062	< 0.1	< 1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4063	< 0.1	< 0.1	< 0.01	< 0.1	< 0.01	NA	< 1
P-4064	< 0.1	< 0.1	< 0.1	< 0.01	< 0.01	NA	NA
P-4065	< 0.1	< 0.1	< 0.1	< 0.01	< 0.01	NA	< 1
P-4066	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	NA	NA
P-4067	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4068	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4069	>1	> 1	> 1	> 1	> 1	NA	NA
P-4070	>1	> 1	> 1	> 1	> 1	NA	NA
P-4071	< 0.1	< 0.1	< 0.1	< 0.1	< 0.01	NA	NA
P-4072	< 0.1	< 1	< 0.01	< 0.01	< 0.01	NA	NA
P-4073	< 0.1	< 1	< 0.1	< 0.01	< 0.01	NA	NA
P-4074	< 1	< 1	< 0.1	< 0.1	< 0.01	NA	NA
P-4075	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4076	< 0.1	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4077	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4078	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4079	< 0.1	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4080	< 0.1	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4081	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA

P-4082	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4083	< 0.1	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4084	< 0.01	< 1	< 0.1	< 0.01	< 0.01	NA	< 10
P-4085	< 1	> 1	< 1	NA	< 0.1	NA	NA
P-4086	NA	NA	< 0.01	NA	NA	NA	NA
P-4087	< 1	> 1	< 1	< 0.1	< 0.01	NA	NA
P-4088	< 0.1	< 1	< 0.1	< 0.1	< 0.01	NA	NA
P-4089	< 0.1	< 1	< 1	< 0.1	< 0.01	NA	< 10
P-4090	< 0.1	< 1	< 0.1	< 0.01	< 0.01	NA	< 1
P-4091	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 0.1
P-4092	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4093	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4094	< 0.1	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4095	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4096	< 0.01	< 1	< 0.01	< 0.01	NA	NA	< 10
P-4097	< 0.1	< 1	< 0.1	< 0.1	NA	NA	< 10
P-4098	< 0.1	< 0.1	< 0.01	< 0.01	NA	NA	< 10
P-4099	< 0.01	< 0.1	< 0.01	< 0.01	NA	NA	< 1
P-4100	< 0.1	< 1	< 0.01	< 0.01	NA	NA	< 1
P-4101	< 0.01	< 1	< 0.1	< 0.01	NA	NA	< 1
P-4102	< 0.01	< 1	< 1	< 0.1	NA	NA	< 1
P-4103	< 0.1	> 1	< 1	> 1	> 1	NA	> 1
P-4104	< 0.1	> 1	< 0.1	< 0.1	< 0.1	NA	< 1
P-4105	< 0.1	> 1	< 0.1	< 1	< 1	NA	< 10

P-4106	< 0.1	< 1	< 0.1	< 0.1	< 0.01	NA	< 1
P-4107	< 0.1	< 1	< 0.1	< 0.1	< 0.01	NA	< 1
P-4108	< 0.1	> 1	< 1	< 1	< 0.1	NA	> 1
P-4109	< 0.1	< 1	< 1	< 1	NA	NA	< 10
P-4110	< 0.1	< 1	>1	> 1	NA	NA	< 10
P-4111	< 0.1	< 1	< 0.01	< 0.01	< 0.01	NA	NA
P-4112	< 0.1	> 1	< 0.1	< 0.1	< 0.01	NA	< 10
P-4113	< 0.01	< 1	< 0.1	NA	NA	NA	NA
P-4114	< 0.01	< 1	< 0.01	NA	NA	NA	NA
P-4115	< 0.01	< 1	< 0.1	< 0.1	< 0.01	NA	NA
P-4116	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4117	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4118	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4119	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4120	< 0.1	< 1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4121	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4122	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4123	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 0.1
P-4124	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 1
P-4125	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	NA
P-4126	< 0.01	< 0.1	< 0.01	< 0.01	< 0.01	NA	< 0.1
P-4127	< 0.01	< 0.1	< 1	< 0.1	< 0.1	NA	< 10
P-4128	< 0.1	< 1	< 1	< 0.1	< 0.1	NA	> 1
P-4129	< 0.1	< 1	< 1	< 0.1	< 0.1	NA	> 10

P-4130	< 0.01	> 1	< 0.1	< 0.01	< 0.01	NA	< 10

[0729] Los compuestos P-3001, P-3004, P-3006, P-3008, P-3013, P-3019, P-3027, P-3036, P-3039, P-3040, P-3041, P-3042, P-3043, P-3044, P-3045, P-4001, P-4004, P-4005, P-4006, P-4007, P-4008, P-4009, P-4010, P-4011, P-4012, P-4013, P-4014, P-4015, P-4016, P-4017, P-4022, P-4023, P-4024, ,P-4025, y P-4026 to P-4130 fueron evaluados y mostraron actividad en el ensayo de diferenciación osteoclástica, donde los compuestos P-3004, P-3006, P-3008, P-3019, P-3027, P-3036, P-3039, P-3041, P-3042, P-4001, P-4004, P-4005, P-4006, P-4007, P-4008, P-4009, P-4010, P-4011, P-4012, P-4013, P-4014, P-4015, P-4016, y P-4023 demonstraron un CI_{50} menor a 0.1 μM en este ensayo.

[0730] Los compuestos también demuestran activiad in vivo en un modelo de esplenomegalia en ratón, donde el crecimiento de la célula BaF3 en el bazo de los ratons desnudos pueden mostrar inhibición bajo tratamiento con el compuesto. Las células BaF3 están diseñadas con cualquier BCR-FMS, BCR-TRK1 o BCR-TRK2 para evaluar los efectos inhibitorios in vivo de la inhibición de las quinasas Fms, TrkA o TrkB, respectivamente. Las células BaF3 se mantienen en medio de crecimiento (RPMI que contiene FBS al 10%, PenStrep al 1%, NEAA al1% , y L-Glutamina al 1%, supplementadon con murina IL-3 al 5% y 1 mg/mL de G418). Cuatro días antes de iniciar, las células 2 x 10^6 células se inoculan en un frasco ventilado T150 usando el medio de cultivo y se incuban a 37 ^oC en CO_2 al 5% por tres días. Un día antes de iniciar, se recolectan las células por centrifugación y se suspenden nuevamente en medio de cultivo sin IL-3. En el día del implante cellular, las células se recolectan por cenfrigación, se enjuagan 3x 20 mL con RPMI, luego se suspenden nuevamente en 5.4 mL de medio y se cuentan, luego se ajustan con RPMI

adicional según lo requerido par producir 5 x 10^7 células/mL. En el día 1, los ratones hembra nu/nu de 5-6 semanas de edad fueron inyectados intravenosamente con células BaF3 inyectando 0.1 mL (5 x 10^6) de células en la vena de la cola (los ratones sin células inyectadas se incluyen como el grupo de control). Los stocks de compuestos en dimetilsulfóxido se almacenan a temperatura ambiente protegidos de la luz. Los stocks diluidos antes de la dosificación, se diluyen con 22 µL del stock de compuesto en 858 µL de diluyente (o 50 µL en 1950 µL) para proporcionar un vehículo de Polisorbato 80 al 1.0%, hidroxipropil metilcélulosa al 0.5%, con dimetilsulfóxido final a 2.5% en todas las suspesiones de dosificación y vehículos de control. Las suspensiones de dosificación se preparan antes de usar, al mezclar por inversión y ultrasonido en un baño de auga para hacer una suspensión uniforme. En los días 10-18, los ratones se tartan con vehículo únicamente o el nivel deseado del compuesto en el vehículo, ~0.2 mL por ratón de 25 gm, una vez al día o por vía oral, o en algunos casos, dos veces por día. En el día 18, a los ratones se les administró una dosis final y dos horas después se tomó la muestra de plasma. Cuatro horas despés de la dosis final, los ratones fuerons sacrificados, se recolectó una muestra de plasma adicional y se removió y se pesó el bazo de los ratones. El peso promedio del bazo en los ratones del grupo de control se comparó con el peso promedio del bazo de los ratones del compuesto de prueba. La inhibición de crecimiento promedio del bazo de los ratones se calculó en 100 x [(peso del bazo del control de vehículo-peso del bazo del compuesto de prueba) / peso del bazo de control del vehículo]. En algunos casos, los compuestos no fueron probados en todos los ensayos o los resultados del ensayo no fueron validos, como lo índica NA en las siguientes tablas.

[0731] La siguiente taba provee los datos que indican el porcentaje de inhibición de crecimiento en el bazo de los compuestos ejemplares indicados (dosificados una vez al día en 10 mg por kg a menos que se indique lo contrario) en el modelo de esplenomegalia en ratones:

# Compuesto	% de inhibición de crecimiento en el bazo		
	Fms	TrkA	TrkB
P-3052	43	NA	NA
P-3010	47	NA	NA
P-3061	48	NA	NA
P-3019	40	NA	14
P-3027	42	NA	2
P-3045	11	NA	NA
P-4052	36	16	41
P-4052*	70	40	91
P-4005	65	25	35
P-4006	55	NA	21
P-4007	28	NA	19
P-4060	24	NA	NA
P-4022	42	NA	33
P-4026	41	NA	NA
P-4027	-1.4	NA	NA
P-4028	86	NA	88
P-4029	66	NA	NA

P-4030	58	NA	50
P-4031	29	NA	NA
P-4053	69	NA	NA
P-4090[#]	38	NA	NA
P-4084	6.2	NA	NA
P-4062	76	NA	NA
P-4061	48	NA	NA
P-4112	9.5	NA	NA
P-4110	30	NA	NA
P-4124	20	NA	NA
P-4120	37	NA	NA
P-4123[#]	14	NA	NA
P-4130	70	NA	NA
P-4128	15	NA	NA

* Dosificados en 30 mg por kg. [#] Dosificados en 5 mg/kg

[0732] Como una indicación de la solubilidad relativa, se evaluó la turbidez de los compuestos en las soluciones acuosas. Para evaluar las posibles propiedades del compuesto en los distintos compartimentos fisiológicos, tales como el estomago, el intestine y la sangre, se usaron distintos búferes acuosos con pH variante. De este modo, cada compuesto se diluye en cuatro búferes fisiológicamente diferentes y la turbidez de la solución se mide por espectrofotometría. Se usa la concentración del compuesto que demuestra la turbidez al forma sufficiente suspension insoluble para elevar la densidad óptica promedio sobre 0.01 en tres longitudes de onda (490, 535, y 650 nm) y definir el límite de la solubilidad del compuesto en ese búfer.

[0733] Los compuestos se disuelven a una concentración de 25 mM en dimetil sulfóxido, luego se diluyen serialmente a 1:1 en una placa de 96 pocillos, diluyendo 10 veces en dimetil sulfóxido puro, siendo el pocillo final de cada fila el blanco del dimetil sulfóxido. En una placa de ensayo, se añaden 99 µL de búfer apropiado a cada pocillo, 1 µL de cada dilución de muestra se añade al búfer, logrando un rango de concentraciones finales en soluciones acuosas que tienen distintos pH. Los búferes usados son Fluido Gástrico Simulado (SGF-f 1.5) 0.5M NaCl, pH 1.5; Fluido Intestinal Simulado (SIF-f 4.5 y f 6.8) 0.05M NaH_2PO_4, pH 4.5 y 6.8; y Búfer Hepes (HEPES-f 7.4) 10 mM HEPES, 150 mM NaCl, pH 7.4. También se evalúan los compuestos de control pirene, estriol y propranolol HCl. Las placas se giran y se mezclan por 1 minuto, y se lee la absorbencia usando un Tecan Safire II para leer las longitudes de onda en el rango visible (490, 535, y 650 nm) en cuatro ubicaciones por pocillo, reflejando el grado de turbidez presente. La densidad óptica promedio de ada longitud de onda en cada pocillo se gráfica vs la concentración del compuesto, y la concentración en la cual la curva cruza un umbral del O.D. de 0.01 para cada longitud de onda se reporta como el resultado del ensayo de turbidez de punto final. El promedio de las tres longitudes de onda se usa para comparar la turbidez de los compuestos. Se considera que los compuestos tienen baja solubilidad si la concentración umbral es de <31.3 µM, la solubilidad es moderada si la concentración umbral es de 31.3 µM a 250 µM, y la solubilidad es alta si la concentración umbral es de >250 µM.

[0734] La siguiente tabla índica la solubilidad relativa (B = baja, M = moderada, A = alta) con base en la concentración umbral de turbidez de cada pH de los compuestos ejemplares de acuerdo con la invención:

Compuesto number	Umbral de turbidez (B, M, A)			
	1.4	4.5	6.8	7.4
P-3049	A	B	B	B
P-3052	A	B	B	B
P-3010	A	B	B	M
P-3059	B	B	B	B
P-3060	M	M	M	M
P-3061	B	B	B	B
P-3014	A	M	M	M
P-3018	A	M	M	M
P-3019	A	B	B	B
P-3039	A	M	M	M
P-3040	M	M	M	M
P-3043	M	M	M	M
P-3044	B	B	B	M
P-3045	M	M	M	B
P-4049	M	M	M	M
P-4050	A	M	M	M
P-4051	M	M	M	M
P-4052	M	M	B	B
P-4005	M	B	B	B

P-4006	A	B	B	B
P-4007	M	B	B	B
P-4008	M	M	M	M
P-4009	A	M	B	B
P-4010	A	M	B	B
P-4059	M	M	M	M
P-4060	M	B	B	B
P-4061	A	M	M	M
P-4014	M	M	M	M
P-4063	M	M	M	M
P-4064	M	A	M	M
P-4017	M	M	M	B
P-4018	M	B	B	B
P-4019	M	B	B	B
P-4022	A	M	B	B
P-4023	A	M	B	B
P-4024	M	B	M	M
P-4025	M	B	B	B
P-4036	A	M	B	B
P-4037	A	M	M	M
P-4048	A	M	M	M
P-4049	A	B	B	B
P-4050	A	B	B	B
P-4051	A	M	M	B

P-4052	B	B	B	B
P-4053	A	M	M	M
P-4054	A	M	M	M
P-4055	M	M	B	B
P-4056	M	M	M	B
P-4057	B	B	B	M
P-4058	M	B	B	B
P-4059	M	B	B	B
P-4060	A	M	M	M
P-4061	M	B	M	M
P-4062	A	B	M	B
P-4063	M	M	M	M
P-4064	A	M	B	B
P-4065	A	M	M	M
P-4066	M	B	B	M
P-4067	A	M	M	M
P-4068	A	M	M	M
P-4069	M	B	M	M
P-4070	A	M	M	M
P-4071	M	M	M	M
P-4072	M	B	B	B
P-4073	M	B	B	B
P-4074	A	M	M	M
P-4075	M	B	B	B

P-4076	M	M	M	B
P-4077	M	B	B	B
P-4078	M	B	B	B
P-4079	A	M	M	M
P-4080	M	M	A	M
P-4081	A	M	A	M
P-4082	M	B	B	B
P-4083	M	M	M	A
P-4084	M	M	M	A
P-4087	A	M	M	M
P-4088	A	M	M	M
P-4089	A	M	M	M
P-4090	M	M	M	M
P-4091	A	M	M	M
P-4092	M	M	M	M
P-4093	A	B	B	B
P-4094	A	B	M	M
P-4095	M	M	M	M
P-4096	A	B	B	B
P-4097	M	B	B	B
P-4098	A	B	M	M
P-4099	A	B	B	B
P-4100	A	M	M	M
P-4101	M	B	B	B

P-4102	A	M	M	M
P-4103	B	M	M	M
P-4104	M	B	B	B
P-4105	M	M	M	M
P-4106	M	M	B	M
P-4107	M	M	M	M
P-4108	H	M	M	M
P-4109	B	B	B	B
P-4110	M	B	B	B
P-4111	A	B	B	B
P-4112	M	M	M	H
P-4114	A	B	B	B
P-4115	A	M	M	M
P-4116	A	M	M	M
P-4117	A	B	B	B
P-4118	A	M	M	B
P-4119	A	M	M	B
P-4120	B	M	M	M
P-4121	A	A	A	A
P-4122	A	B	M	B
P-4123	A	L	L	L
P-4124	M	L	L	M
P-4125	A	L	L	L
P-4127	A	M	M	M

P-4128	A	M	M	M
P-4129	A	M	M	M
P-4130	A	M	M	M

[0735] Las enzimas CIP (Citocromo P450) son las principales enzimas metabolizantes de fármacos presentes en el hígado. La inhibición de la actividad de la enzima CIP (CI_{50}) para cada CIP1A2, CIP2C19, CIP2C9, CIP2D6, CIP3A4(BFC) y CIP3A4(BQ) se determina para los compuestos, donde la inhibición del metabolismo de un sustrato conocido lleva a una disminución en la fluorescencia del producto metabolizado. La fluorescencia del producto se monitorea como una función de la concentración del compuesto.

[0736] Los compuestos se desuelven en dimetil sulfóxido a una concentración de 100 mM. Estos se diluyen en 1 µL a 82 µL de acetonitrilo. Luego se añade una alícuota de 11 µL de esta solución a 204 µL de la mezcla cofactor (1.3% NADF Solución del Sistema de Regeneración A, 1.04% NADF Solución del Sistema de Regeneración B de BD Biosciences, 5% acetonitrilo y 0.05% dimetil sulfóxido). Luego estas se diluyen a1:1 (mezcla de cofactor 160 µL a160 µL) para un total de 10 puntos. Se despensa una alícuota de 10 µL de esta mezcla final en placas de ensayo de 384 pocillos y se incuban por 10 minutos a 37 ºC. Se añade la mezcla de la enzima y el sustraA (10 µL; 0.5 pmol CIP1A2/5 µM CEC; 1.0 pmol CIP2C9/75 µM MFC; 0.5 pmol CIP2C19/25 µM CEC; 1.5 pmol CIP2D6/1.5 µM AMMC; 1.0 pmol CIP3A4/50 µM BFC; o 1.0 pmol CIP3A4/40 µM BQ) a estas placas de ensayo. Las placas de ensayo se incuban a 37 ºC (CIP1A2-15 men; CIP2C9-45 men;

CIP2C19, 2D6 y 3A4-30 men) y se leen en un lector de placas Tecan Safire 2+ (CIP1A2, 2C19 y 3A4 409 ex/460 em; CIP2C9 y 2D6 409 ex/530 em). La concentración de la señal versus el compuesto se usa para determinar el CI_{50}. Las enzimas y los sustratos para este ensayo se obtienen de BD Biosciences. Mientras que se involucran otros factores para determinar los efectos del CIP *in vivo*, los compuestos preferiblemente tienen valores de CI_{50} de >5 μM, más preferiblemente valores de CI_{50} de > 10 μM.

[0737] La siguiente tabla indica la inhibición del CIP para los compuestos ejemplares de acuerdo con la invención:

# Compuesto	Cip CI_{50} (μM)					
	1A2	2C19	2C9	2D6	3A4(BFC)	3A4(BQ)
P-3049	> 10	> 10	> 10	> 10	> 10	> 10
P-3052	> 10	5-10	> 10	> 10	> 10	> 10
P-3006	> 10	> 10	> 10	> 10	> 10	NA
P-3008	> 10	< 5	5-10	> 10	5-10	NA
P-3009	> 10	< 5	> 10	> 10	5-10	NA
P-3010	> 10	> 10	> 10	> 10	> 10	> 10
P-3059	> 10	> 10	> 10	> 10	> 10	> 10
P-3060	> 10	> 10	> 10	> 10	> 10	> 10
P-3061	5-10	< 5	> 10	> 10	> 10	> 10
P-3018	> 10	> 10	> 10	> 10	< 5	> 10
P-3019	> 10	< 5	> 10	> 10	> 10	> 10

P-3039	> 10	> 10	> 10	> 10	> 10	NA
P-3040	> 10	> 10	> 10	> 10	> 10	> 10
P-3041	> 10	> 10	> 10	> 10	5-10	> 10
P-3043	> 10	> 10	> 10	> 10	> 10	> 10
P-3044	> 10	> 10	> 10	> 10	> 10	> 10
P-3048	> 10	< 5	> 10	> 10	> 10	> 10
P-3049	> 10	> 10	> 10	> 10	> 10	> 10
P-3050	> 10	> 10	> 10	> 10	> 10	> 10
P-3051	> 10	> 10	> 10	> 10	> 10	> 10
P-3052	> 10	5-10	5-10	> 10	> 10	> 10
P-3053	> 10	> 10	> 10	> 10	> 10	> 10
P-4049	> 10	< 5	> 10	> 10	> 10	NA
P-4050	> 10	> 10	> 10	> 10	> 10	> 10
P-4051	> 10	> 10	> 10	> 10	> 10	> 10
P-4052	> 10	> 10	> 10	> 10	> 10	> 10
P-4005	> 10	> 10	> 10	> 10	> 10	> 10
P-4006	> 10	> 10	> 10	> 10	> 10	> 10
P-4007	> 10	> 10	> 10	> 10	> 10	> 10
P-4008	> 10	> 10	> 10	> 10	5-10	> 10
P-4009	> 10	5-10	> 10	> 10	> 10	> 10
P-4010	> 10	> 10	> 10	> 10	> 10	> 10
P-4059	> 10	> 10	5-10	> 10	5-10	> 10
P-4060	> 10	> 10	> 10	> 10	> 10	> 10
P-4061	> 10	> 10	< 5	> 10	> 10	> 10

P-4014	> 10	> 10	5-10	< 5	5-10	> 10
P-4063	> 10	> 10	> 10	> 10	> 10	> 10
P-4064	> 10	> 10	> 10	> 10	> 10	> 10
P-4017	> 10	> 10	> 10	> 10	> 10	> 10
P-4018	> 10	< 5	> 10	> 10	5-10	> 10
P-4019	> 10	5-10	> 10	> 10	5-10	> 10
P-4022	> 10	5-10	> 10	5-10	5-10	> 10
P-4023	> 10	< 5	> 10	5-10	< 5	> 10
P-4024	> 10	> 10	> 10	> 10	< 5	> 10
P-4025	> 10	5-10	> 10	> 10	< 5	> 10
P-4028	> 10	5-10	5-10	> 10	> 10	> 10
P-4029	> 10	> 10	> 10	> 10	> 10	> 10
P-4030	> 10	5-10	> 10	> 10	> 10	> 10
P-4031	> 10	> 10	> 10	< 5	> 10	> 10
P-4036	5-10	5-10	5-10	> 10	5-10	5-10
P-4037	> 10	> 10	5-10	> 10	5-10	5-10
P-4041	5-10	< 5	5-10	> 10	> 10	5-10
P-4047	> 10	> 10	> 10	> 10	> 10	> 10
P-4048	> 10	> 10	> 10	> 10	> 10	> 10
P-4049	> 10	5-10	5-10	> 10	> 10	> 10
P-4050	> 10	> 10	> 10	> 10	> 10	> 10
P-4051	> 10	> 10	> 10	> 10	> 10	> 10
P-4052	> 10	> 10	> 10	> 10	> 10	> 10
P-4053	> 10	> 10	> 10	> 10	> 10	> 10

P-4054	> 10	> 10	> 10	> 10	> 10	> 10
P-4055	< 10	< 10	> 10	> 10	> 10	> 10
P-4056	> 10	5-20	> 10	> 10	> 10	> 10
P-4057	> 10	> 10	> 10	> 10	> 10	> 10
P-4058	> 10	> 10	> 10	> 10	> 10	> 10
P-4059	> 10	> 10	5-10	> 10	> 10	> 10
P-4060	> 10	> 10	> 10	> 10	> 10	> 10
P-4061	> 10	> 10	> 10	> 10	> 10	> 10
P-4062	> 10	> 10	> 10	> 10	> 10	> 10
P-4063	> 10	> 10	> 10	> 10	> 10	> 10
P-4064	> 10	> 10	> 10	> 10	> 10	> 10
P-4065	> 10	> 10	> 10	> 10	> 10	> 10
P-4066	> 10	> 10	> 10	> 10	> 10	5-10
P-4067	> 10	5-10	> 10	> 10	> 10	> 10
P-4068	> 10	> 10	> 10	> 10	> 10	> 10
P-4069	> 10	5-10	> 10	> 10	5-10	> 10
P-4070	> 10	> 10	> 10	> 10	> 10	> 10
P-4071	> 10	> 10	> 10	> 10	> 10	> 10
P-4072	> 10	< 10	5-10	5-10	> 10	> 10
P-4073	> 10	5-10	> 10	> 10	> 10	> 10
P-4074	> 10	5-10	> 10	> 10	> 10	> 10
P-4075	> 10	5-10	> 10	> 10	> 10	> 10
P-4076	> 10	5-10	> 10	> 10	> 10	> 5
P-4077	5-10	5-10	> 10	> 10	> 10	> 10

P-4078	5-10	> 10	> 10	> 10	> 10	> 10
P-4079	> 10	5-10	> 10	> 10	> 10	> 10
P-4080	> 10	> 10	> 10	> 10	> 10	> 10
P-4081	> 10	> 10	> 10	> 10	> 10	> 10
P-4082	> 10	> 10	> 10	> 10	> 10	5-10
P-4083	> 10	> 10	> 10	> 10	> 10	> 10
P-4084	> 10	5-10	> 10	> 10	> 10	> 10
P-4087	> 10	> 10	> 10	> 10	> 10	> 10
P-4088	> 10	> 10	> 10	> 10	> 10	> 10
P-4089	> 10	> 10	> 10	> 10	> 10	> 10
P-4090	> 10	> 10	> 10	> 10	> 10	> 10
P-4091	> 10	> 10	> 10	> 10	> 10	> 10
P-4092	< 5	< 5	< 5	< 5	> 10	> 10
P-4093	> 10	> 10	> 10	> 10	> 10	> 10
P-4094	< 5	< 5	< 5	< 5	> 10	> 10
P-4095	> 10	> 10	> 10	> 10	> 10	> 10
P-4096	< 5	< 5	< 5	< 5	> 10	5-10
P-4097	< 5	< 5	< 5	< 5	> 10	> 10
P-4098	< 5	< 5	< 5	< 5	> 10	> 10
P-4099	< 5	< 5	< 5	< 5	> 10	< 5
P-4100	< 5	< 5	< 5	< 5	> 10	> 10
P-4101	> 10	5-10	5-10	> 10	> 10	> 10
P-4102	< 5	< 5	< 5	< 5	> 10	> 10
P-4103	< 5	> 10	> 10	> 10	> 10	> 10

P-4104	> 10	5-10	> 10	> 10	> 10	> 10
P-4105	> 10	> 10	> 10	> 10	> 10	> 10
P-4106	< 5	< 5	< 5	< 5	> 10	> 10
P-4107	< 5	< 5	< 5	< 5	> 10	> 10
P-4108	< 5	< 5	< 5	< 5	> 10	> 10
P-4109	> 10	5-10	5-10	> 10	> 10	> 10
P-4110	< 5	< 5	< 5	< 5	> 10	> 10
P-4111	> 10	5-10	5-10	> 10	> 10	5-10
P-4112	< 5	< 5	< 5	< 5	> 10	> 10
P-4113	> 10	> 10	> 10	> 10	> 10	> 10
P-4114	> 10	> 10	> 10	> 10	> 10	> 10
P-4115	< 5	< 5	< 5	< 5	> 10	> 10
P-4116	> 10	> 10	> 10	> 10	> 10	> 10
P-4117	5-10	> 10	5-10	> 10	> 10	> 10
P-4118	> 10	> 10	> 10	> 10	> 10	> 10
P-4119	> 10	> 10	> 10	> 10	> 10	> 10
P-4120	< 5	< 5	< 5	< 5	> 10	> 10
P-4121	> 10	5-10	> 10	> 10	> 10	> 10
P-4122	> 10	> 10	5-10	> 10	> 10	> 10
P-4123	> 10	> 10	> 10	> 10	> 10	> 10
P-4124	< 5	< 5	< 5	< 5	> 10	> 10
P-4125	> 10	> 10	> 10	> 5	> 10	> 10
P-4126	< 5	> 10	> 10	> 10	< 10	5-10
P-4127	> 10	5-10	> 10	> 10	< 5	< 5

P-4128	> 10	> 10	> 10	> 10	> 10	> 10
P-4129	> 10	> 10	5-10	5-10	< 5	< 5
P-4130	> 10	< 5	> 10	> 10	< 5	> 10

[0738] Las propiedades farmacocinéticas de los compuestos (incluyendo cualquier forma sólida o Formulaciones de estos) se evaluaron en ratas macho Sprague Dawley o perros macho Beagle. Las ratas fueron dosificadas diariamente con el compuesto mediante inyecciones IV con catésteres yugulares implantados quirúrgicamente o mediante alimentación oral forzada (PO). Cada compuesto se prepara como una solución stock de 20 mg/mL en dimetil sulfóxido, la cual se diluye adicionalmente proporcionar el stock de dosificación en la concentración deseada para las Formulaciones IV o PO. Para la dosificación IV, el stock de dosificación se diluye en una mezcla 1:1:8 de Solutol ®:etanol: agua. Para la dosificación PO, el stock de dosificación se diluye en metilcelulosa1%. En un formato de casete (o cada compuesto, forma sólida del mismo o Formulación del mismo se prepara individualmente, los compuestos se diluyen a 0.5 mg/mL cada uno por dosificación IV y a 0.4 mg/mL cada uno por dosificación PO y dosificados a 1 mg/kg (2mL/kg) o 2 mg/kg (5 mL/kg), respectivamente. Para los animales dosificados por IV, se recolectan muestras de sangre de la vena de la cola con anticoagulante de heparina de litio a 5, 15, 30, y 60 minutos y 4, 8, y 24 horas después de la dosificación cada día. Para los animales dosificados por PO, se recolectan muestras de sangre de la vena de la cola con anticoagulante de heparina de litio a 30 minutos, 1, 2, 4, 8 y 24 horas después de la dosificación cada día. Los perros son dosificados diariamente mediante cápsulas orales con una Formulación

apropiada de 50 mg/mL. Las muestras de sangre de la vena cefálica se recolectan con anticoagulante de heparina de litio a 30 minutos, 1, 2, 4, 8 y 24 horas después de la dosificación cada día. Todas las muestras se procesan al plasma y se congelan para el análisis de cada compuesto mediante LC/MS/MS. Los niveles de plasma son graficados como una función de tiempo para evaluar la ABC (ng*hr/mL). Los compuestos de acuerdo a la presente invención preferiblemente muestran propiedades farmacocinéticas mejoradas relativas a los compuestos anteriormente descritos, es decir, tienen valores sustancialmente más altos para una o más ABC, Cmax y vida media relativa a los compuestos anteriormente descritos.

[0739] Los análisis de penetración del compuesto en el cerebro pueden evaluarse de forma similar. Cada compuesto se prepara como una solución stock de 100 mg/mL stock en dimetil sulfóxido, así como los compuesto de control en atenolol en 100 mg/mL y antipirina a 50 mg/mL. En un formato de cassette, se combinan hasta tres compuestos de prueba, junto con el atenolol y la antipirina, 180 μL de cada uno, y se añaden a 17.1 mL de metilcélulosa al 1%. Los compuestos están en una supsensión que se administra en una sola dosis (10 mL por kg de peso corporal) para los 2 grupos de ratas CD (8-9 semanas, n=3 por grupo) por alimentación oral forzada, y un grupo adicioanl de ratas se dosificó con el vehículo únicamente. Uno grupo de las ratas tratadas con el compuesto fue sacrificado 2 horas después de la dosificación, el otro grupo a las 6 horas. El Plasma se recolectó en Li-heparina en se recolectaron los cerebros, cortados en los hemisferios derecho e izquierdo, se pesaron y se congelaron inmediatamente. Las muestras de homogenato de cerebro (30%) y de plasma fueron evaluadas usando un aparato de diálisis de equilibrio de 96 pocillos con corte de membrana de 5K MW (The Nest Group, Inc.) según el

protocolo del vendedor con las muestran en un lado de la membrana y un volumen igual de 1XPBS en el otro lado. El aparato se incubó toda la noche a 37 ºC con un rotador de placas (Te Nest Group, Inc.). Las concentraciones del compuesto en ambos lados se analizan mediante LC/MS/MS para calcular la recuperación del balance de masa. La concentración del lado PBS se cálcula usando una curva estándar generada para cada compuesto. La concentración PBS es la concentración del compuesto libre, mientras que el lado con la muestra biológica muestra la concentración en plasma o cerebro.

Ejemplo 17: Eficacia de los Compuestos en Combinación con los agentes quimioterapéuticos de cuidado estándar en cuatro líneas de células cancerígenas humanas.

[0740] Compuestos de la invención, tal como los compuestos de la fórmula I, en combinación con el agente quimioterapéutico estándar, tal como 5-fluorouracilo, carboplatino, dacarbazina, gefitinib, oxaliplatino, paclitaxel, SN-38, temozolomida, o vinblastina, pueden evaluarse en cuanto a su efectividad al eliminar células tumorales humanas. Dichos ensayos son conocidos en el arte, por ejemplo, como lo describe la Aplicación de Patente Estadounidense con Serial Número 11/473,347, cuya divulgación se incorpora aquí por referencia con respecto a dichos ensayos.

[0741] Todas las patentes y referencias aquí citadas en la especificación son indicativas del nivel de habilidad de aquellos con habilidad en el arte a la que pertenece la invención, y se incorporan mediante referencia en su totalidad, incluyendo cualquier tabla y figura, a la misma magnitud como si cada referencia haya sido incorporada mediante referencia en su totalidad individualmente.

[0742] Una persona con habilidad en el arte podría apreciar fácilmente que la presente invención está bien adaptada para lograr los fines y ventajas mencionadas, así como aquellos inherentes en ese sentido. Los métodos, varianzas y composiciones aquí descritas como las represenqueivas de las formas de realización preferidas son ejemplos y no son limitantes del alcance de la invención. Los cambios y otros usos para aquellos con habilidad en el arte, quienes se incluyen en la esencia de la invención, se definirán por el alcance de las reivindicaciones.

[0743] La invención aquí descrita de forma ilustrativa puede ser practicada en ausencia de cualquier elemento o elementos, limitación o limitaciones que no se divulguen específicamente. De este modo, por ejemplo, en cada caso aquí descrito los términos “que consiste”, “que comprende” y “que consiste de” pueden ser reemplazados con cualquiera de los otros dos términos. Así que para la forma de realización de la invención que use uno de los términos, la invención también incluye otra forma de realización donde uno de estos términos es reemplazado. En cada forma de realización, los términos tienen su significado establecido. Así, por ejemplo, una forma de realización puede incluir un método “que consiste” de una serie de pasos, otra forma de realización podría incluir un método “que consiste esencialmente de” los mismos pasos, y una tercera forma de realización podría incluir un método “que comprende” los mismos pasos. Los términos y expresiones

han sido usadas como términos de descripción y no de limitación, y que no se tiene la intención de que el uso de dichos términos y expresiones se excluyan de cualquier equivalente de las características mostradas o descritas o porciones de estas, pero se reconoce que son posibles varias modificaciones dentro del alcance de la invención reivindicada. De modo que, debe entenderse que aunque la presente invención se ha divulgado específicamente mediante las formas de realización preferidas y las características opcionales, la modificación y variación de los conceptos aquí divulgados pueden ser reclasificados por aquellos con habilidad en el arte, y se considera que tales modificaciones están dentro del alcance de esta invención ya que se define por las reivindicaciones anexas.

[0744] Adicionalmente, cuando las características o aspectos de la invención se describen en términos de grupos Markush u otras alternativas de agrupación, aquellos con habilidad en el arte reconocerán que la invención se describe en términos de cualquier miembro individual o subgrupo de miembros del grupo Markush u otro grupo.

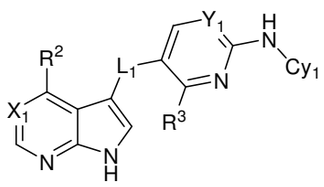
[0745] También, a menos que se indique lo contrario, donde se suministran varios valores numéricos para las formas de realización, se describen formas de realización adicionales al tomar cualquiera de los 2 valores diferentes como puntos finales de un rango. Dichos rangos también están dentro del alcance de la invención descrita.

[0746] De modo que, las formas de realización adicionales están dentro del alcance de la invención y dentro de las siguientes reivindicaciones.

REIVINDICACIONES

Lo que se reivindica es:

1. Un compuesto que tiene la estructura química de la Fórmula I,



FórmulaI

o una sal, profármaco, solvato o tautómero o esteroisómero del mismo

donde:

X_1 es-N=, -C(H)=, or -C(R^1)= ;

Y_1 es-N= y R^3 es Hidrógeno; o Y_1 es -C(H)= y R^3 es flúor o cloro;

L_1 es -C(H_2)- or -C(O)-;

Ci_1 es Cicloalquilo opcionalmente sustituido con uno o más R^4, el fenil opcionalmente sustituido con uno o más R^5, o heteroaril de 5 o 6 miembros opcionalmente sustituido en un átomo de carbono disponible con uno o más R^6 y opcionalmente sustituido en un átomo de nitrógeno disponible con R^7;

donde X_1 es -C(R^1)=, R^2 es Hidrógeno;

donde X_1 es-N= o -C(H)=, R^2 es seleccionado del grupo que consiste de hidrógeno, cicloalquilo, alquilo inferior opcionalmente sustituido con uno o más R^8, -N(R^{9a})(R^{9b}), y -O-R^9;

R^1 es flúor, cloro, o alquilo inferior opcionalmente substitituido con uno o más flúor;

cada R^4 es independientemente seleccionado del grupo que consiste de flúor, -OH, alquilo inferior opcionalmente sustituido con uno o más flúor, y alcoxi inferior opcionalmente sustituido con uno o más flúor;

cada R^5 es independientemente seleccionado del grupo que consiste de flúor, cloro, -O-R^{10}, -S-R^{11}, -S(O_2)-R^{12}, y alquilo inferior opcionalmente sustituido con uno o más R^{13};

cada R^6 es independientemente seleccionado del grupo que consiste de flúor, cloro, bromo, cicloalquilo, alquilo inferior opcionalmente sustituido con uno o más flúor, y alcoxi inferior opcionalmente sustituido con uno o más flúor; o dos R^6 unidos a átomos de carbono adyacentes del anillo heteroarilo forman un anillo cicloalquilo fusionado;

R^7 es Cicloalquilo, alcoxi inferior o alquilo inferior opcionalmente sustituido con uno o más flúor;

R^8 es flúor o alcoxi inferior opcionalmente sustituido con uno o más flúor;

R^{9a} es H y R^{9b} es seleccionado del grupo que consiste de (i) H, alquilo inferior, alquilo inferior sustituido con uno o más flúor, alquilo inferior sustituido con alcoxi inferior o alquilo inferior sustituido con hidroxil y (ii) cicloalquilo, cicloalquiloalquilo, heterocicloalquilo, heterocicloalquiloalquilo, arilalquilo, heteroarilalquilo, cada uno de los cuales es opcionalmente sustituido con uno a tres miembros seleccionados de alquilo inferior, haloalquilo,alcoxi inferior o flúor; o

R^{9a} y R^{9b} junto con nitrógeno al cual se adhieren forman un anillo de 5 a 6 miembros que tiene de 0 a 1 heteroátomos seleccionados de O, N o S, cada uno de los cuales es opcionalmente sustituido con uno a tres miembros seleccionados de alquilo inferior, haloalquilo,alcoxi inferior o flúor;

R^9 es alquilo inferior, alquilo inferior sustituido con uno o más flúor, o alquilo inferior sustituido con alcoxi inferior ;

cada R^{10}, R^{11} y R^{12} son independientemente alquilo inferior opcionalmente sustituido con uno o más flúor; y

cada R^{13} es independientemente seleccionado del grupo que consiste de flúor, -OH, y alcoxi inferior opcionalmente sustituido con uno o más flúor.

2. El compuesto de la reivindicación **1**, donde X_1 es N, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

3. El compuesto de la reivindicación **2**, donde L_1 es CH_2, Y_1 es CH y R^3 es F, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

4. El compuesto de la reivindicación **2**, donde L_1 es CH_2, Y_1 es N y R^3 es F, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

5. El compuesto de la reivindicación **2**, donde L_1 es -C(=O)-, Y_1 es CH y R^3 es F, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

6. El compuesto de la reivindicación **2**, donde L_1 es -C(=O)-, Y_1 es N y R^3 es F, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

7. El compuesto de la reivindicación **1**, donde X_1 es-$C(R^1)$=, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

8. El compuesto de la reivindicación **7**, donde L_1 es CH_2, Y_1 es CH y R^3 es F, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

9. El compuesto de la reivindicación **7**, donde L_1 es -C(=O)-, Y_1 es CH y R^3 es F, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

10. El compuesto de la reivindicación **7**, donde L_1 es-CH_2-, Y_1 es N y R^3 es F, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

11. El compuesto de la reivindicación **7**, donde L_1 es -C(=O)-, Y_1 es N y R^3 es F, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

12. El compuesto de la reivindicación **1**, donde X_1 es N y R^2 es -N(R^{9a})(R^{9b}), o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

13. El compuesto de cualquiera de las reivindicaciones **1-12**, donde Ci_1 es Cicloalquilo opcionalmente sustituido con uno o más R^4, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

14. El compuesto de la reivindicación **13**, donde Ci_1 es Ciclopropil, ciclobutil, ciclopentil, ciclohexil, ciclopentil, cada uno de los cuales es opcionalmente sustituido con de 1 a 3 R^4, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

15. El compuesto de cualquiera de las reivindicaciones **1-12**, donde Ci_1 es el fenil opcionalmente sustituido con uno o más R^5, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

16. El compuesto de cualquiera de las reivindicaciones **1-12**, donde Ci_1 es 5 o 6-membered heteroaril opcionalmente sustituido en un átomo de carbono disponible con uno o más R^6 y opcionalmente sustituido en un átomo de nitrógeno disponible con R^7, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

17. El compuesto de la reivindicación **16**, donde Ci_1 es 3-piridil, 2-pirrolil, 3-pirrolil o 4-pirazolil, opcionalmente sustituido en un átomo de carbono disponible con de 1 a 3 R^6 y opcionalmente sustituido en un átomo de nitrógeno disponible con R^7, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

18. El compuesto de la reivindicación **16** or **17**, donde cada R^6 es independientemente seleccionados del grupo que consiste de flúor, cloro, bromo, cicloalquilo, alquilo inferior opcionalmente sustituido con de uno a tres flúor, y alcoxi inferior opcionalmente sustituido con uno a tres flúor; o dos R^6 unidos a átomos de carbono adyacentes del anillo heteroarilo forman un anillo cicloalquilo fusionado, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

19. El compuesto de cualquiera de las reivindicaciones **1**-**12**, donde R^{9a} es H y R^{9b} es seleccionados de H, alquilo inferior, alquilo inferior sustituido con hidroxi, alquilo inferior sustituido conalcoxi inferior , alquilo inferior sustituido con 1 a 3 grupos de flúor, cicloalquilo opcionalmente sustituido con alquilo inferior o uno a tres flúor, cicloalquiloalquilo opcionalmente sustituido con alquilo inferior o uno a tres sustitutos de flúor, heterocicloalquilo opcionalmente sustituido con alquilo inferior, heterocicloalquiloalquilo, arilalquilo opcionalmente sustituido con de 1 a 3 miembros seleccionados de alquilo inferior, flúor o haloalquilo y el heteroarilalquilo opcionalmente sustituido con de uno a tres miembros seleccionados de alquilo, flúor o haloalquilo.

20. El compuesto de la reivindicación **19**, donde R^{9a} es H y R^{9b} es seleccionado de (i) H, metil, etil, t-butil, propil, isopropil, 2-butil, n-butil, 2-hidroxi-2-metilpropil, 2-metoxietil, 3-metoxipropil, 2,2,2-triflúoroetil, o 4-metoxibutil y (ii) ciclopropil, ciclobutil, ciclopentil, ciclohexil, ciclopropilmetil, ciclobutilmetil, ciclopentilmetil, cicloheximetil, bencil, 1-metilbencil, 4,4-diflúorociclohexil, 2-tetrahidrofuranoilmetil, 4-piperadinil, 3-piridil, 2-piridil o 4-piridil, cada uno de los cuales es opcionalmente sustituido con de 1 a 3 miembros seleccionados de alquilo inferior, alcoxi inferior , flúor o CF_3, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

21. El compuesto de cualquiera de las reivindicaciones **1-12** , donde -$N(R^{9a})(R^{9b})$ es 1-piperadinil, 4-morfolinil, 1-piperazinil o 1-pirrolidinil, cada uno de los cuales es opcionalmente sustituido con uno a tres miembros seleccionados de alquilo inferior, haloalquilo, alcoxi inferior o flúor, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

22. El compuesto de acuerdo con la reivindicación **1**, donde el compuesto es seleccionado de cualquiera de los compuestos P-3049, P-3051 a P-3053, P-4049 a P-4032 y P-4036 a P-4202 establecidos en la Tabla 1 o Tabla 2 , o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

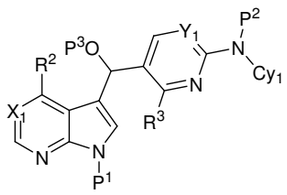
23. Una composición que incluye un compuesto de acuerdo con cualquiera de las reivindicaciones **1-22**, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo; y un portador farmacéuticamente aceptable.

24. Una composición que incluye un compuesto de cualquiera de las reivindicaciones **1**-**22**, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo, un portador farmacéuticamente aceptable y un agente quimioterapéutico.

25. Un kit que incluue un compuesto de acuerdo con cualquiera de las reivindicaciones **1**-**22**, o una sal, profármaco, solvato o tautómero o esteroisómero del mismo.

26. Un método para preparar un compuesto de la fórmula I de acuerdo con la reivindicación **1**, dicho método incluye:

conectar un compuesto de la Fórmula (II):

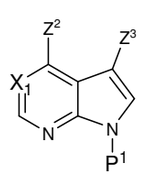


(II)

con un agente bajo condiciones suficientes para preparar el compuesto de la fórmula(I), donde P^1 y P^2 son cada uno de forma independiente un grupo protector de amino y P^3 es H o un grupo protector.

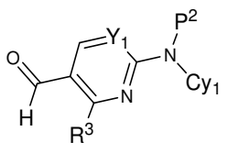
27. Un método para preparar un compuesto de la fórmula II de acuerdo con la reivindicación **26**, dicho método incluye:

conectar un compuesto de la Fórmula (III):



(III)

con un compuesto de la Fórmula IV:



IV

bajo condicionos suficientes para formar un compuesto de la Fórmula(II), donde Z^2 es Cl, Br o R^2 y Z^3 es yodo o un grupo saliente.

28. Un método para tratar un sujeto que sufre o está en riesgo de sufrir una enfermedad o condición, que incluye la administración de una cantidad efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones **1-22**, donde la enfermedad o condición se selecciona del grupo que consiste de artritis reumatoide, osteoartritis, osteoporosis, peri-osteolisis prostética, esclerosis sistémica, desórdenes desmielinizantes, esclerosis múltiple, síndrome de Charcot Marie Toot, esclerosis amiotrófica lateral, Enfermedad de Alzheimer, Enfermedad de Parkinson, isquemia global, colitis ulcerativa, enfermedad de Crohn, púrpura trombocitopénica inmune, aterioesclerosis, lupus erimatoso sistémico, mielopreparación para trasplante autólogo, rechazo de trasplante, glomerulonefritis, nefritis intersticial, nefritis lúpica, necrosis tubular, nefropatía diabética, hipertrofia renal, diabetes tipo I, dolor agudo, dolor inflamatorio, dolor neuropático, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de seno, cáncer de próstata, cáncer pancreático, cáncer de pulmón, cáncer de ovario, gliomas, glioblastoma, neurofibromatosis, metástasis ósea, metástasis cerebral, tumores estromales gastrointestinales, y tumores de células gigantes.

29. Un método para tratar un sujeto que sufre o está en riesgo de sufrir una enfermedad o condición, que incluye la administración de una cantidad

efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones **1-22**, donde la enfermedad o condición se selecciona del grupo que consiste de artritis reumatoide, osteoartritis, osteoporosis, peri-osteolisis prostética, esclerosis múltiple, Enfermedad de Alzheimer, Enfermedad de Parkinsonr, isquemia global, hipertrofia renal, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de seno, cáncer de próstata , cáncer pancreático , glioblastoma, neurofibromatosis, metástatis cerebral, y tumores estromales gastrointestinales.

30. Un método para tratar un sujeto que sufre o está en riesgo de sufrir una enfermedad o condición, que incluye la administración de una cantidad efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones **1-22**, donde la enfermedad o condición se selecciona del grupo que consiste de cáncer pancreático , cáncer de próstata , y mieloma múltiple.

31. Use de un compuesto de acuerdo con cualquiera de las reivindicaciones **1-22** para la Preparación de un medicamento para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de artritis reumatoide, , osteoartritis, osteoporosis, osteolisis periprostética, esclerosis sistémica, desórdenes desmielinizantes, esclerosis múltiple, Síndrome de Charcot Marie Tooth, esclerosis lateral amiotrópica, enfermedad de Alzheimer, enfermedad de Parkinson, isquemia global, colitis ulcerativa, enfermedad de Crohn, purpura trombocitopénica inmune, arterioesclerosis, lupus erimatoso sistémico, mielopreparación para trasplante autólogo, rechazo de trasplante, glomerulonefritis, nefritis intersticial, nefritis lúpica, necrosis tubular, nefropatía diabética, hipertrofia renal, diabetes tipo I, dolor

agudo, dolor inflamatorio, dolor neuropático, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de seno, cáncer de próstata, cáncer pancreático, cáncer de pulmón, cáncer de ovario, gliomas, glioblastoma, neurofibromatosis, metástasis ósea, metástasis cerebral, tumores estromales gastrointestinales, y tumores de células gigantes.

32. para la Preparación de un medicamento para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de artritis reumatoide, osteoartritis, osteoporosis, peri-osteolisis prostética, esclerosis múltiple, Enfermedad de Alzheimer, Enfermedad de Parkinsonr, isquemia global, hipertrofia renal, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de seno, cáncer de próstata , cáncer pancreático , glioblastoma, neurofibromatosis, metástatis cerebral, y tumores estromales gastrointestinales.

33. Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones **1-22** para la preparación de un medicamento para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de cáncer pancreático , cáncer de próstata , y mieloma múltiple.

34. Un compuesto de acuerdo con cualquiera de las reivindicaciones **1-22** para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de artritis reumatoide, , osteoartritis, osteoporosis, osteolisis periprostética, esclerosis sistémica, desórdenes desmielinizantes, esclerosis múltiple, Síndrome de Charcot Marie Tooth, esclerosias lateral amiotrópica, enfermedad de Alzheimer, enfermedad de Parkinson, isquemia global, colitis ulcerativa, enfermedad de Crohn, purpura trombocitopénica inmune,

arterioesclerosis, lupus erimatoso sistémico, mielopreparación para trasplante autólogo, rechazo de trasplante, glomerulonefritis, nefritis intersticial, nefritis lúpica, necrosis tubular, nefropatía diabética, hipertrofia renal, diabetes tipo I, dolor agudo, dolor inflamatorio, dolor neuropático, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de seno, cáncer de próstata, cáncer pancreático, cáncer de pulmón, cáncer de ovario, gliomas, glioblastoma, neurofibromatosis, metástasis ósea, metástasis cerebral, tumores estromales gastrointestinales, y tumores de células gigantes.

35. Un compuesto de acuerdo con cualquiera de las reivindicaciones **1-22** para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de artritis reumatoide, osteoartritis, osteoporosis, peri-osteolisis prostética, esclerosis múltiple, Enfermedad de Alzheimer, Enfermedad de Parkinsonr, isquemia global, hipertrofia renal, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de seno, cáncer de próstata , cáncer pancreático , glioblastoma, neurofibromatosis, metástatis cerebral, y tumores estromales gastrointestinales.

36. Un compuesto de acuerdo con cualquiera de las reivindicaciones **1-22** para el tratamiento de una enfermedad o condición seleccionada del grupo que consiste de cáncer pancreático, cáncer de próstata, y mieloma múltiple.

RESUMEN

Se describen los compuestos y sales, formulaciones, conjugados, derivados, formas y usos de los mismos. En ciertos aspectos y formas de realización, los compuestos descritos o sales, formulaciones, conjugados, derivados, formas del mismo son una o más proteínas quinasas activas tipo Fms, Kit, Flt3, TrkA, TrkB y TrkC. También se describen los métodos de uso de los mismos para tratar enfermedades y condiciones, incluyendo enfermedades y condiciones asociadas con la actividad de una o más de las quinasas Fms, Kit, Flt3, TrkA, TrkB y TrkC, incluyendo artritis reumatoide, , osteoartritis, osteoporosis, osteolisis periprostética, esclerosis sistémica, desórdenes desmielinizantes, esclerosis múltiple, Síndrome de Charcot Marie Tooth, esclerosias lateral amiotrópica, enfermedad de Alzheimer, enfermedad de Parkinson, isquemia global, colitis ulcerativa, enfermedad de Crohn, purpura trombocitopénica inmune, arterioesclerosis, lupus erimatoso sistémico, mielopreparación para trasplante autólogo, rechazo de trasplante, glomerulonefritis, nefritis intersticial, nefritis lúpica, necrosis tubular, nefropatía diabética, hipertrofia renal, diabetes tipo I, dolor agudo, dolor inflamatorio, dolor neuropático, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de seno, cáncer de próstata, cáncer pancreático, cáncer de pulmón, cáncer de ovario, gliomas, glioblastoma, neurofibromatosis, metástasis ósea, metástasis cerebral, tumores estromales gastrointestinales, y tumores de células gigantes.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 October 2011 (27.10.2011)

PCT

(10) International Publication Number
WO 2011/133637 A3

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61K 31/519* (2006.01)
C07D 487/04 (2006.01) *A61P 19/00* (2006.01)
A61K 31/437 (2006.01) *A61P 25/00* (2006.01)
A61K 31/506 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/US2011/033192

(22) International Filing Date:
20 April 2011 (20.04.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/326,626 21 April 2010 (21.04.2010) US

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

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

Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
9 February 2012

WO 2011/133637 A3

(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 one or more of Fms, Kit, Flt3, TrkA, TrkB and TrkC kinase protein. Also described are methods of use thereof to treat diseases and conditions, including diseases and conditions associated with activity of one or more of Fms, Kit, Flt3, TrkA, TrkB and TrkC, including rheumatoid arthiritis, osteoarthritis, osteoporosis, periprosthetic osteolysis, systemic sclerosis, demyelinating disorders, multiple sclerosis, Charcot Marie Tooth syndrome, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, global ischemia, ulcerative colitis, Crohn's disease, immune thrombocytopenic purpura, atherosclerosis, systemic lupus erythematosis, myelopreparation for autologous transplantation, transplant rejection, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, renal hypertrophy, type I diabetes, acute pain, inflammatory pain, neuropathic pain, acute myeloid leukemia, melanoma, multiple myeloma, breast cancer, prostate cancer, pancreatic cancer, lung cancer, ovarian cancer, gliomas, glioblastoma, neurofibromatosis, osteolytic bone metastases, brain metasteses, gastrointestinal stromal tumors, and giant cell tumors.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/033192

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/04(2006.01)i, C07D 487/04(2006.01)i, A61K 31/437(2006.01)i, A61K 31/506(2006.01)i, A61K 31/519(2006.01)i, A61P 19/00(2006.01)i, A61P 25/00(2006.01)i, A61P 35/00(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 471/04; C07D 487/04; C07D 487/02; A61K 31/519

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

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

eKOMPASS(KIPO internal), Google, PubMed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2007-0225306 A1 (CHOI, H.-S. et al.) 27 September 2007 See claims 1, 6.	1-17,19-22,26-27
A	US 2006-0058324 A1 (CAPRARO, H.-G. et al.) 16 March 2006 See claim 1.	1-17,19-22,26-27
A	US 2007-0161666 A1 (BLUMENKOPF, T. A. et al.) 12 July 2007 See the entire document.	1-17,19-22,26-27

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

☒ See patent family annex.

* Special categories of cited documents:

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

"E" earlier 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 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
19 DECEMBER 2011 (19.12.2011)	**19 DECEMBER 2011 (19.12.2011)**
Name and mailing address of the ISA/KR Korean Intellectual Property Office Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer LEE, Dong Wook Telephone No. 82-42-481-8163

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/033192

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.: 28-30
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 28-30 pertain to a method for treatment of the human by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

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.: 18, 23-25, 28-36
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 addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

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

Information on patent family members

International application No.

PCT/US2011/033192

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